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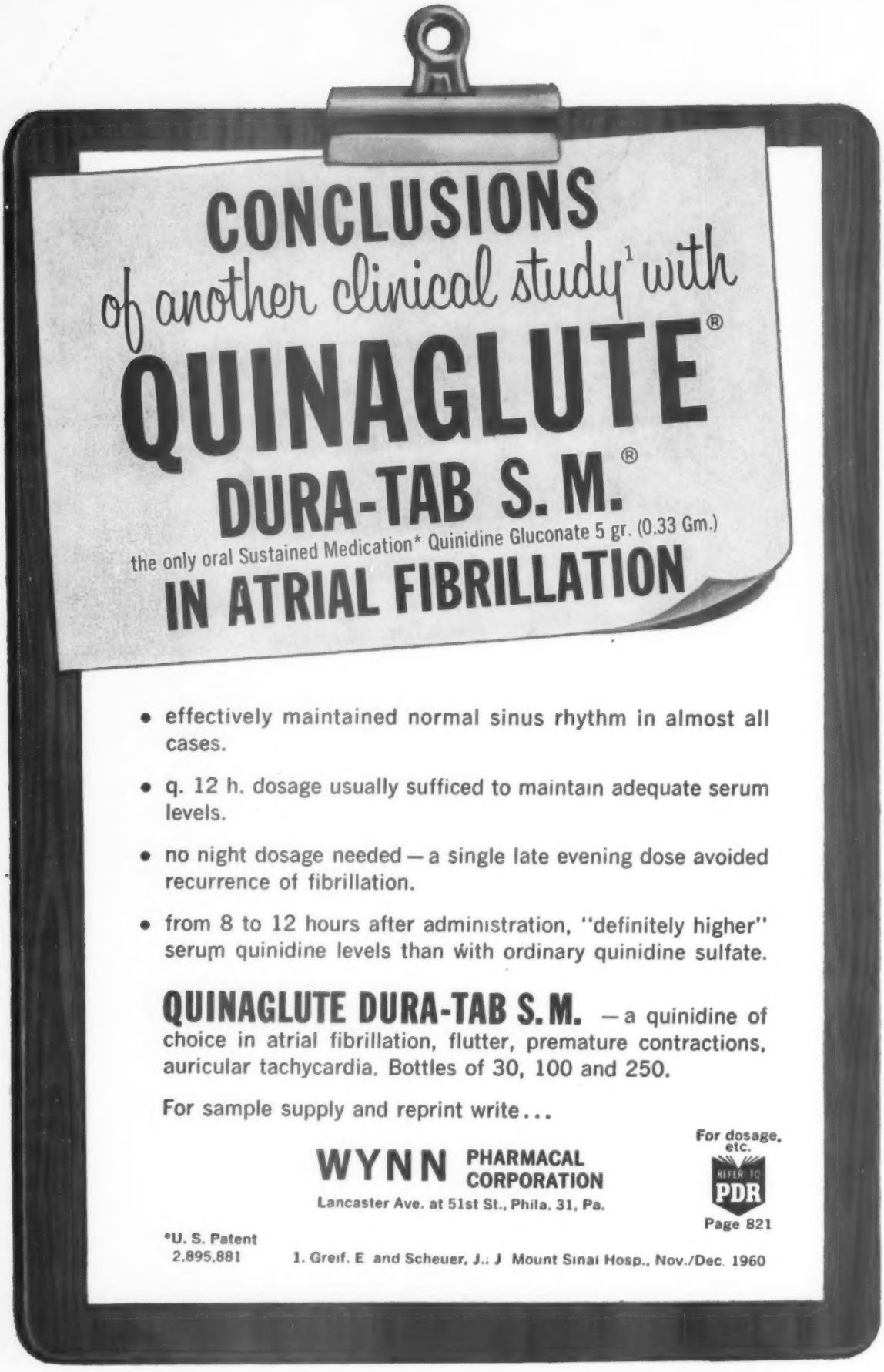
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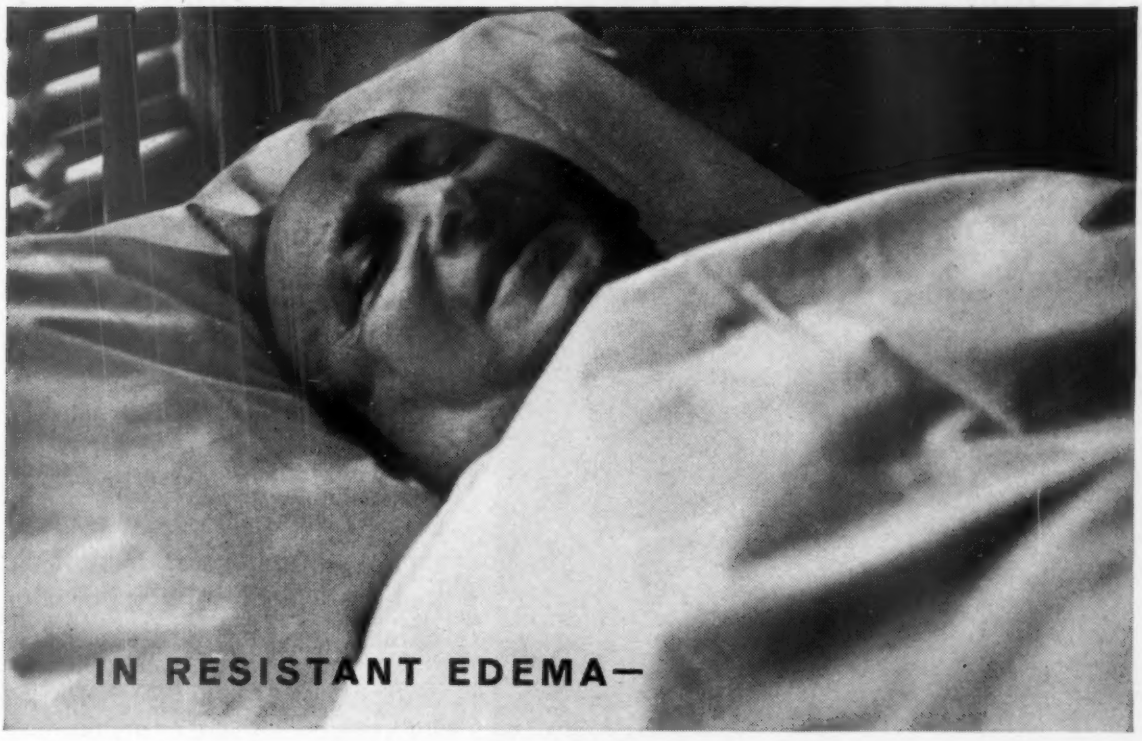
*U. S. Patent 2,895,881
1. Greif, E and Scheuer, J.: J Mount Sinai Hosp., Nov./Dec. 1960



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References: 1. Parsons, W. B., Jr.: Arch. Int. Med. *107*:71, 1961. 2. Parsons, W. B., Jr.: Personal communication. 3. Taylor, C. B., *et al.:* Illinois M.J. *119*:80, 1961. 4. Christensen, N. A., *et al.:* J.A.M.A. *177*:546, 1961.

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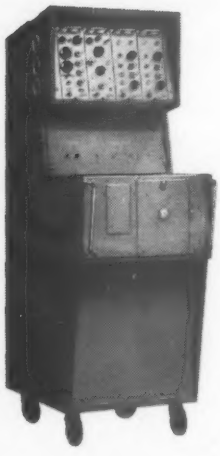

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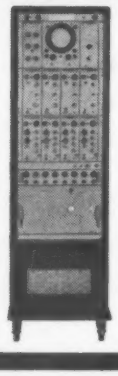

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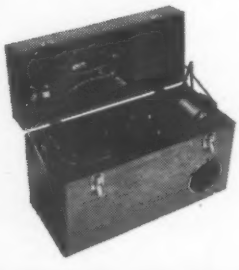

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The American Journal of Cardiology

Volume VIII NOVEMBER 1961 Number 5

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Recognizing Compensated Shock 611

DAVID W. IRVING AND ELIOT CORDAY

Clinical Studies

Hypertrophic Subaortic Stenosis. Clinical and Hemodynamic Studies with Special Reference to Pulse Contour Measurement 614

GUY M. BOITEAU AND BERTRAM J. ALLENSTEIN

Reporting on three cases of hypertrophic subaortic stenosis, these investigators emphasize the diagnostic value of the unusual pulse contour. In this anomaly a prolonged ejection time and a large secondary systolic wave, representing the subaortic muscular obstruction, were observed. Clinically, a diamond-shaped holosystolic murmur at the fifth left intercostal space and a good aortic sound were heard. Interestingly enough, two of the three patients had had subacute bacterial endocarditis.

Cardiac Involvement in a Peculiar Form of Paramyloidosis 624

EDUARDO COELHO AND J. CORTEZ PIMENTEL

Primary amyloidosis affecting the heart produces serious cardiac insufficiency and heart failure. Involvement of the heart may also occur in paramyloidosis characterized by a familial incidence and peripheral neuropathy. Skin biopsy is the best diagnostic test. The Congo red test is usually negative in these conditions.

Ventricular Aneurysm. Fourteen Cases Subjected to Cardiac Bypass Repair Using the Pump Oxygenator 633

DON W. CHAPMAN, KAMEL AMAD AND DENTON A. COOLEY

Fourteen patients, with the help of a temporary cardiopulmonary bypass, underwent excision of aneurysms of the left ventricle. Clinical findings, physiologic data and surgical technic are described. Cardiac catheterization in twelve patients prior to surgery revealed reduction in cardiac output and significant pulmonary hypertension. After operation, cardiac function improved and the eleven survivors of surgery showed clinical benefits.

Experimental Study

Phenol-Talc Procedure for Myocardial Revascularization. Experimental and Clinical Studies 649

IRA HUGH FRIEDMAN, ALBERT B. LOWENFELS, SOL GELMAN AND JERE W. LORD, JR.

When indicated, the phenol-talc cardiopexy improves the myocardial blood supply with minimal surgical risk. Measurements in dogs demonstrate that it brings 4.3 cc. of new blood per minute to the myocardium suffering from surgically-induced ischemia.

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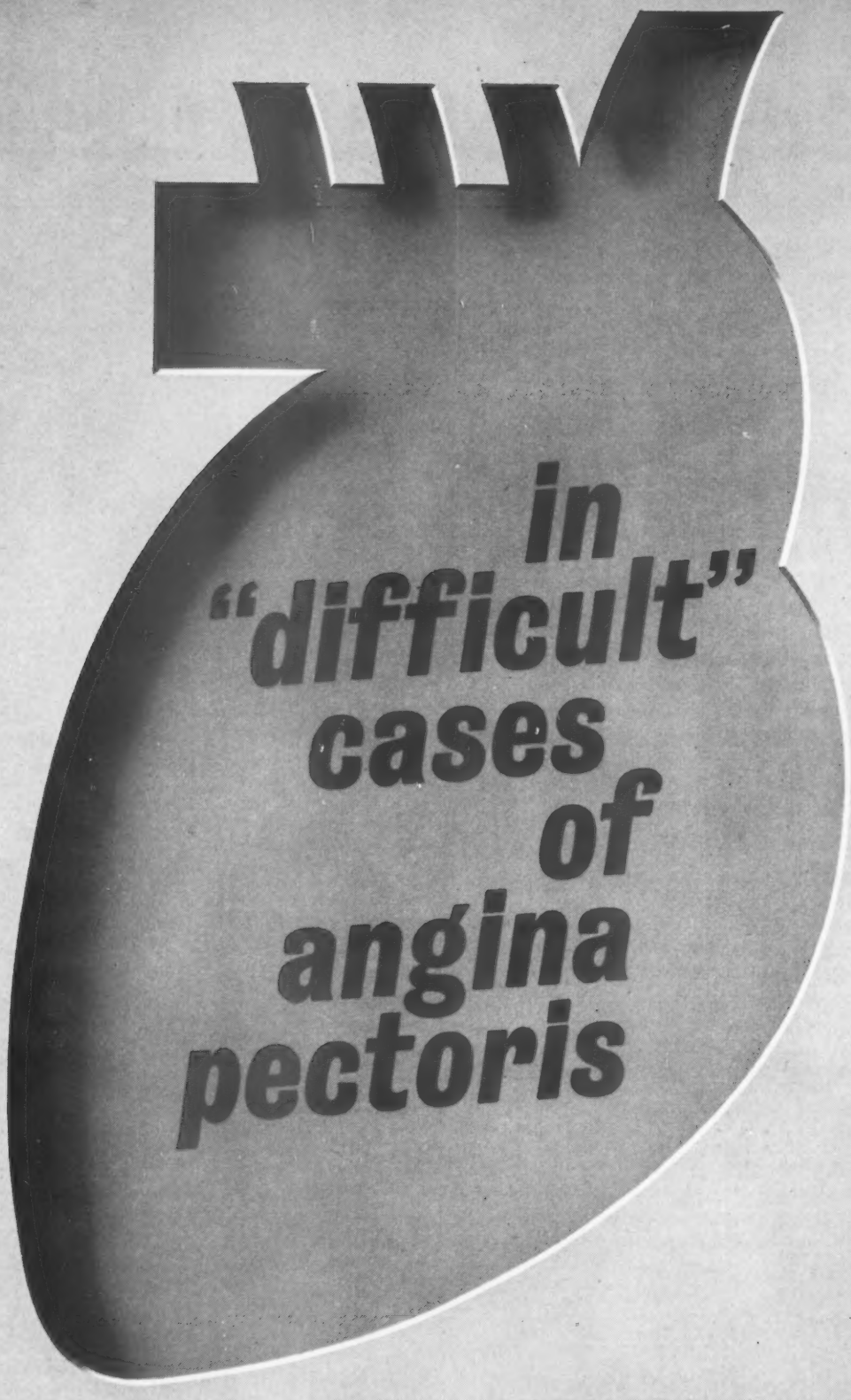

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reduces nitroglycerin requirements[2,3]

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References: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, **Virginia M. Month.**, 87:23, 1960. 4. T. Winsor and P. Zarco, **Angiology**, 11: (Part 2), 67, 1960. 5. G. C. Griffith, **Clin. Med.**, 6:1555, 1959. 6. G. C. Griffith, **Dis. Nerv. System**, 21 (Suppl.), 101, 1960.

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New Method

Localization of Right to Left Shunts with an Intravascular Polarographic Anode Sensitive to Ascorbic Acid 659

SAMUEL KAPLAN, LELAND C. CLARK, JR., F. KATHRYN EDWARDS, MARIAN E. GALLAHER AND R. PHYLLIS FOX

An intravascular polarographic anode sensitive to ascorbic acid is described. It appears useful in detecting and localizing right to left shunts.

Case Reports

Complete Interruption of the Aorta. 664

M. CONCEPCIÓN RUIZ VILLALOBOS, DELFINA P. DE BALDERRAMA, JUAN LOPEZ Y LOPEZ AND MIGUEL CASTELLANOS

A Teflon prosthesis was successfully used to connect the left subclavian artery to the distal aorta in a 14 year old boy with complete interruption of the aortic isthmus, a patent ductus arteriosus and probable ventricular septal defect.

Hemorrhagic Rheumatoid Pericarditis 670

JERE B. STERN AND HAROLD J. SOBEL

Hemorrhagic pericarditis is a rare but frequently fatal complication of rheumatoid arthritis. In the two recorded cases, including this one, terminal cardiac tamponade due to hemorrhagic pericarditis followed the abrupt cessation of steroid therapy. Acute fibrinosis and fibrous pericarditis are more common, and fortunately less fatal, during the course of rheumatoid arthritis.

Generalized Glycogenosis. 675

HARRY STOECKLE, ARMOND S. GOLDMAN AND JOHN A. WEBB

Generalized glycogenosis involving the heart, skeletal muscle, liver and brain was found at autopsy in an infant suspected of having congenital heart disease. Glycogen structure and enzyme determinations were within normal limits, but autoglycogenolysis was absent.

Diagnostic Shelf

Concealed Retrograde Conduction 682

LEO SCHAMROTH

Concealed retrograde conduction explains the temporary nodal rhythm with A-V dissociation which followed a ventricular extrasystole.

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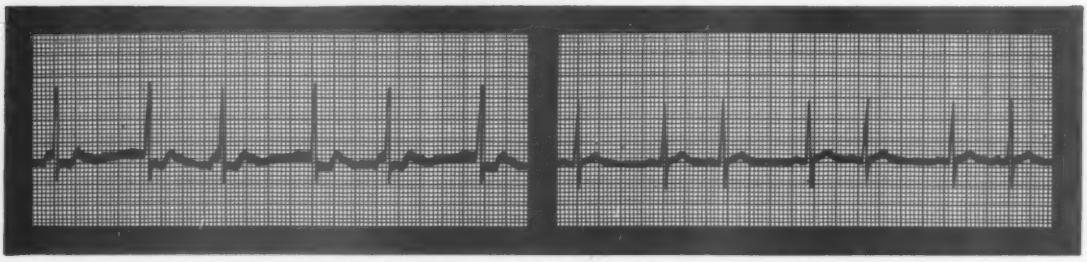
in coronary artery disease

with or without angina

Peritrate is basic for both

because it produces a substantial and sustained increase in myocardial blood flow... without significant change in cardiac output, blood pressure, or pulse rate

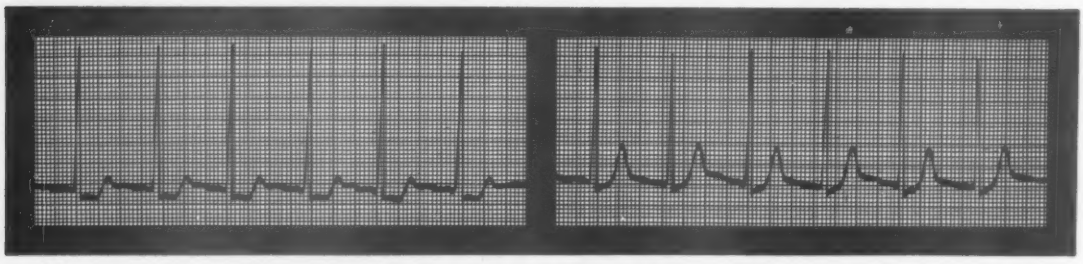
the patient [with] angina*



before **Peritrate**—S-T depression after standard exercise in anginal patient with no history of infarction.

after **Peritrate** (20 mg., administered 4 hours before exercise test). S-T segment near normal.

the postcoronary patient [without] angina*



before **Peritrate**—Abnormal ECG response to standard exercise in postinfarction patient without angina.

after **Peritrate** (20 mg., administered 90 minutes before exercise test). S-T segment near normal.

*Electrocardiograms and case histories on file in the Medical Department, Warner-Chilcott Laboratories.

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Seminar on the Role of Salt in Cardiovascular Hypertension (Part II)

Effect of Salt on the Kidney and the Juxtaglomerular Apparatus 684

LOUIS TOBIAN, JR.

This investigator adduces evidence that the juxtaglomerular apparatus of the kidney, by its stretch receptor function, serves as an important volume-regulating system. He also cites evidence implicating this system in the production of renal hypertension.

Effect of Sodium Chloride on the Thyroid Gland and on Iodide Metabolism 688

HENRI ISLER

In rats, prolonged administration of sodium chloride increases renal loss of iodides, thereby decreasing the uptake of iodine by the thyroid and consequently the synthesis and secretion of thyroid hormone. The pituitary gland is then stimulated to produce thyrotropic hormone which may, in turn, produce goiter in these rats fed sodium chloride.

Activity of Thyroid Gland during Development of Renal Hypertension in Rats . . . 694

MELVIN J. FREGLY AND JOE V. GONZALEZ

Thyroid gland activity in rats with renal hypertension increases sharply as the systolic blood pressure reaches 150 to 160 mm. Hg. It then, apparently, further elevates the blood pressure to hypertensive levels.

Plasma Corticosterone Levels and Salt Intake in Experimental Hypertension in the Rat 700

FLOYD R. SKELTON AND PAUL M. HYDE

The mean maximum plasma corticosterone concentration 1 hour after subcutaneous injection of the steroid into uninephrectomized adrenalectomized rats was not significantly different from that observed in normal rats 1 hour after exposure to nonspecific stress. The data in these and other experiments suggest that the significant differences observed between the blood pressures of animals receiving 2.5 mg. and 1.25 mg. of corticosterone twice daily is due to differences in salt consumption rather than to the steroid.

Experimental Hypercholesterolemia from Chronic Excess Salt Feeding 705

LEWIS K. DAHL

Prolonged feeding of excess salt to female rats and dogs over a period of several years frequently elevates the plasma cholesterol concentration, often markedly. Enhanced intestinal absorption, increased synthesis or decreased degradation are possible mechanisms not yet confirmed. There is no indication that excess salt consumption is related to atherogenesis.

Panel Discussion 714

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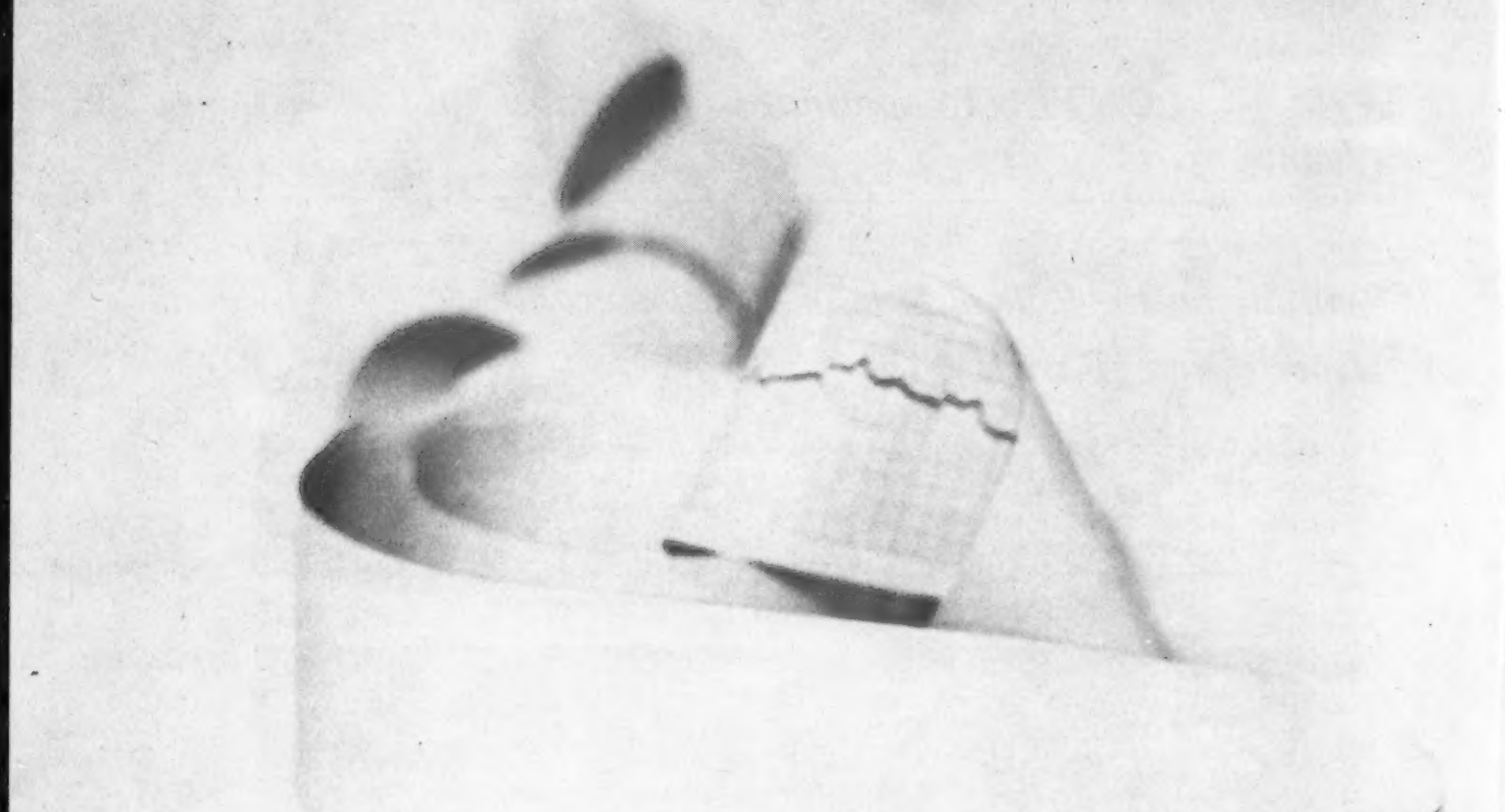

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VOLUME EIGHT NUMBER FIVE

Some Observations on the Role of Added Supplements of Sodium and Lithium in the Pathophysiology of Corticoid and Metacorticoid Hypertension in the Rat . 719

CHARLES E. HALL AND OCTAVIA HALL

Severe hypertensive cardiovascular disease occurs in rats treated with DCA while drinking a solution of LiCl. Hypertension did not develop in the animals whose growth was stunted by the toxic effects of the lithium. Metacorticoid hypertension can develop in the hypophysectomized rat. A sustained hypertension in the intact rat follows prolonged NaCl excess intake. Withdrawal of sodium excess does not affect the hypertensive state once it is induced in the rats.

The Enhanced Hypertensogenic Effect of Sea Salt over Sodium Chloride 726

LEWIS K. DAHL AND MARTHA HEINE

Rats consuming sea salt for 1 year had greater hypertension than rats eating sodium chloride. The responsible elements have not yet been identified.

Effect of Potassium Nitrate Solution on Blood Pressure of Rats 732

MELVIN J. FREGLY

Drinking KNO_3 solutions by rats increased the systolic blood pressures and the ratio of organ weight to body weight of kidneys, testis and adrenals. The same concentrations of NaCl and KNO_3 produced similar physiologic responses in rats.

The Role of Potassium and Its Relation to Sodium in the Regulation of Blood Pressure 737

S. CHARLES FREED

The dynamic role of potassium in the regulation of blood pressure is influenced by the content of sodium in arterial tissue. The sodium-potassium ratio of arterial tissue varies inversely with the change in blood pressure level.

Autoregulation of Blood Flow in Peripheral Vascular Beds 741

WENDELL N. STAINSBY AND EUGENE M. RENKIN

Autoregulation of blood flow is the phenomenon whereby changes in perfusing pressure of a tissue or organ produce relatively small changes in blood flow. Experiments indicate this phenomenon is a regular, characteristic property of skeletal muscle. The myogenic theory of autoregulation remains most acceptable but there is some evidence for a metabolically-linked stimulus such as bradykinin or some other blood-borne substance.

Effect of Dietary Sodium: Potassium Ratio on Body Content of Sodium and Potassium in Rats. 748

JANET LEMLEY-STONE, WILLIAM J. DARBY AND GEORGE R. MENEELY

Rats fed diets high in NaCl with added K lived longer and had less hypertension than those on the same high levels of Na without added K. The addition of K to diets containing more than 2 per cent Na also prevented the increased Na space, $(Na)_E$ and tissue Na which otherwise occurred.

Panel Discussion 754

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†Russek, H.I.: Am J. Cardiol. *3*:547 (April) 1959.

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Isordil produces a dramatic decrease in the incidence and severity of Angina Pectoris[1]

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- With its high solubility, comparable to that of nitroglycerin, Isordil has a much faster onset of action than do some older therapies. For example, with Isordil the therapeutic lag caused by the low solubility of PETN is avoided. Isordil starts to work within 15 to 30 minutes; as fast as two minutes if partially dissolved in the mouth before swallowing.
- Because the liver metabolizes it very slowly, Isordil has a longer duration of action—about 4 to 6 hours.

References: 1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet 81:112 (Mar.) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology 12:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine 2:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society 36:14 (Dec.) 1960. 5. Berry, J. W.; Carney, R. and Lankford, H.: Clinical Experiences with Isosorbide Dinitrate (Isordil®), Angiology 12:254 (June) 1961. 6. Sherber, D. A. and Gelb, I. J.: The Clinical Pharmacology of Isosorbide Dinitrate: A Unique, New Nitrated Polyalcohol, ibid. 7. Joseph, L. G. and Mancini, A.: Isosorbide Dinitrate in Angina Pectoris, ibid.

Reprints, literature and professional samples available on request. Consult direction circular or Physicians' Desk Reference before prescribing.

FOR ANGINA PECTORIS

Isordil®

(ISOSORBIDE DINITRATE)

Also Available: ISORDIL WITH PHENOBARBITAL, the accepted sedative for the relief of anxiety in heart patients.

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Sometime this month the 100,000,000th injection of Mercuhydrin will be given. We can interpret this figure in many ways . . . First of all, in terms of lives prolonged or saved . . . in terms of therapeutic advances, for the modern approach to therapy of congestive heart failure owes much to the long-established efficacy and safety of this drug. The published literature, clinical and experimental, is enormous and continuous. After more than 15 years Mercuhydrin remains the pharmacologic standard for the clinical comparison of diuretics. And as a pharmaceutical preparation, Mercuhydrin has not been surpassed in its stability and reliability. Lakeside is indeed proud of Mercuhydrin.

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MERCUHYDRIN®, brand of meralluride sodium, Lakeside. **Supplied in 1 cc. and 2 cc. ampuls in boxes of 12, 25 and 100, and 10 cc. rubber capped, multiple dose vials in boxes of 6, 25 and 100. Needs no refrigeration. *Contraindications:* Acute nephritis and intractable oliguric states.**

Full thiazide therapy that goes easy on the potassium

"ONCE A DAY—EVERY DAY"

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Methyclothiazide, Abbott

Enduron gives you full measure of the familiar thiazide benefits: diuresis, sodium and chloride elimination, antihypertensive action. It is potent (peak dose is 10 mg., versus 2000 mg. for chlorothiazide, for example). One 10-mg. dose yields sodium excretion equal or superior to previously available thiazides in *any* size dose. Long-acting, too: every tablet delivers 24 hours' continuous therapy, so that rarely does your patient require more than one daily dose.

Yet with all this efficacy, Enduron is surprisingly sparing of serum potassium. The *single* daily dose causes but a *single* temporary peak of potassium loss, compared with multiple peaks of multi doses. Moreover, Enduron's effect on potassium has upper limits; doubling the single dose from 5 to 10 mg. approximately doubles the output of sodium—yet under this same condition, potassium output increases little or not at all.

Thus Enduron produces less potassium excretion per unit of sodium excreted, so that depletion rarely becomes a problem.

Use Enduron with patients who have mild to moderate hypertension, or patients with edema (as in congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, or steroid therapy). Observe its convenience and effectiveness. *We predict you'll be glad you used it.*

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NEW THIAZIDE RAUWOLFIA ANTIHYPERTENSIVE

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Of course, Enduronyl can't *cure* your patients' hypertension... but it certainly can simplify treatment. It enables you to provide the fullest advantages of thiazide and rauwolfia —in a single convenient agent—and you'll need just *one* dose daily. Note these two components:

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Together, these two components provide even greater antihypertensive action than with either alone. Blood pressure starts down steadily, and improvement should be substantial within 10 days. Use Enduronyl and see. Full literature available promptly on request: *contact Abbott Laboratories, North Chicago, Illinois.*

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1. Biegeleisen, H. L.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

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controlled disintegration capsules

PENTRITOL—Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective therapy for and prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown superior results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity for physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol®-B Tempules®, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

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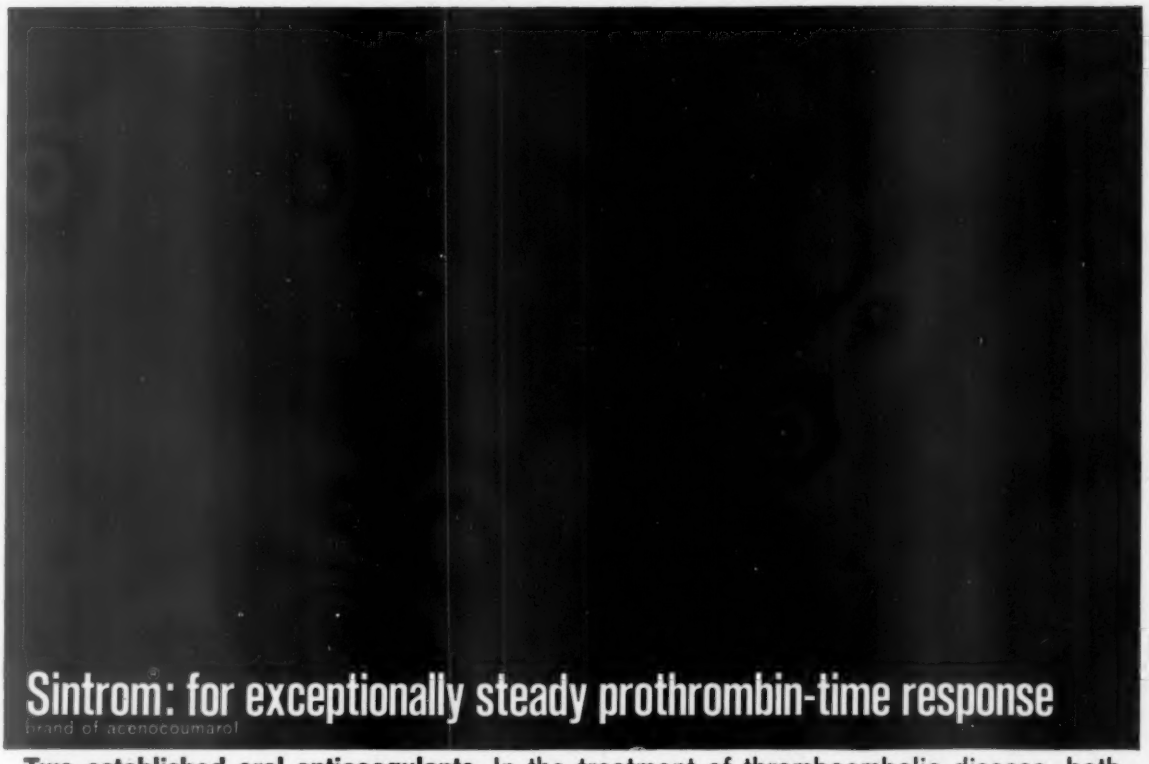

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brand of acenocoumarol

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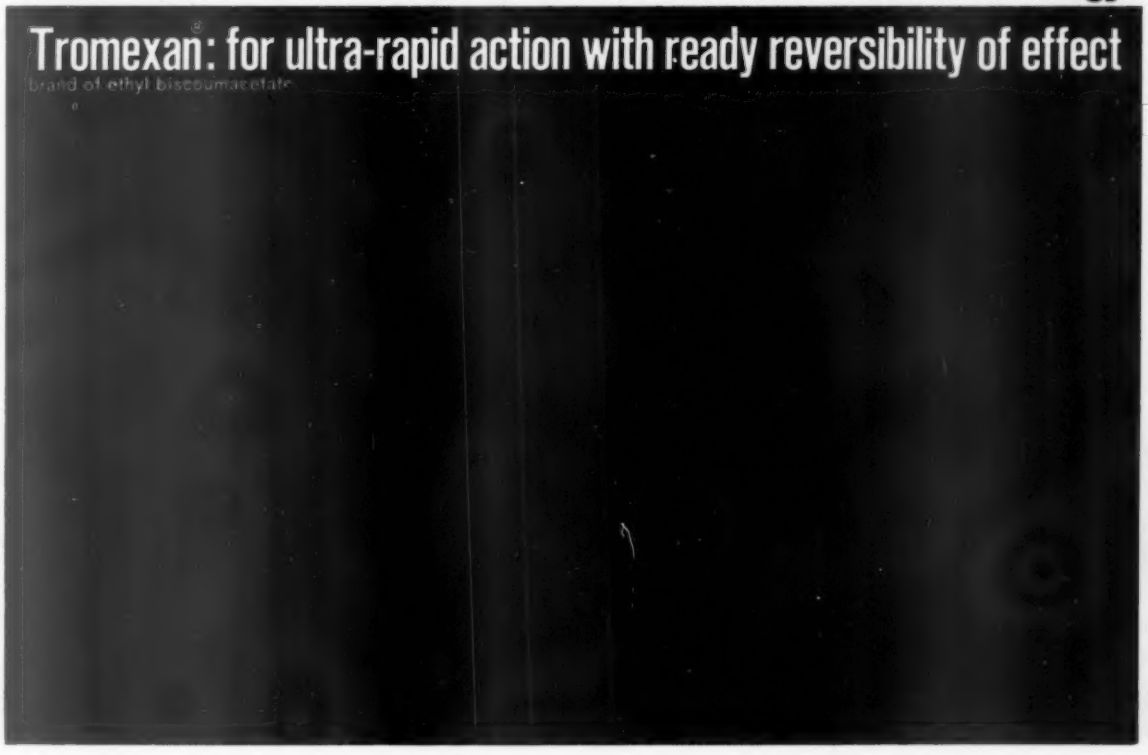
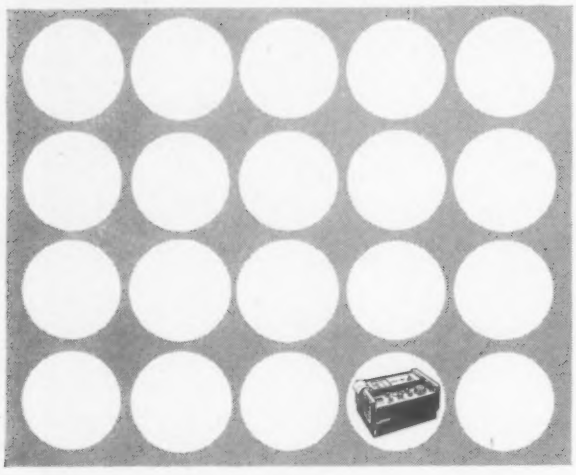
Tromexan®, brand of ethyl biscoumacetate, is supplied as single-scored tablets of 150 and 300 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York SI/TR-662-61 **Geigy**



Tromexan®: for ultra-rapid action with ready reversibility of effect

brand of ethyl biscoumacetate



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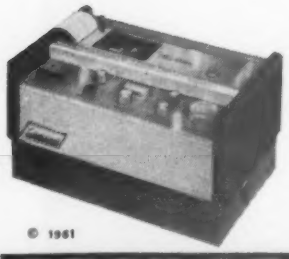

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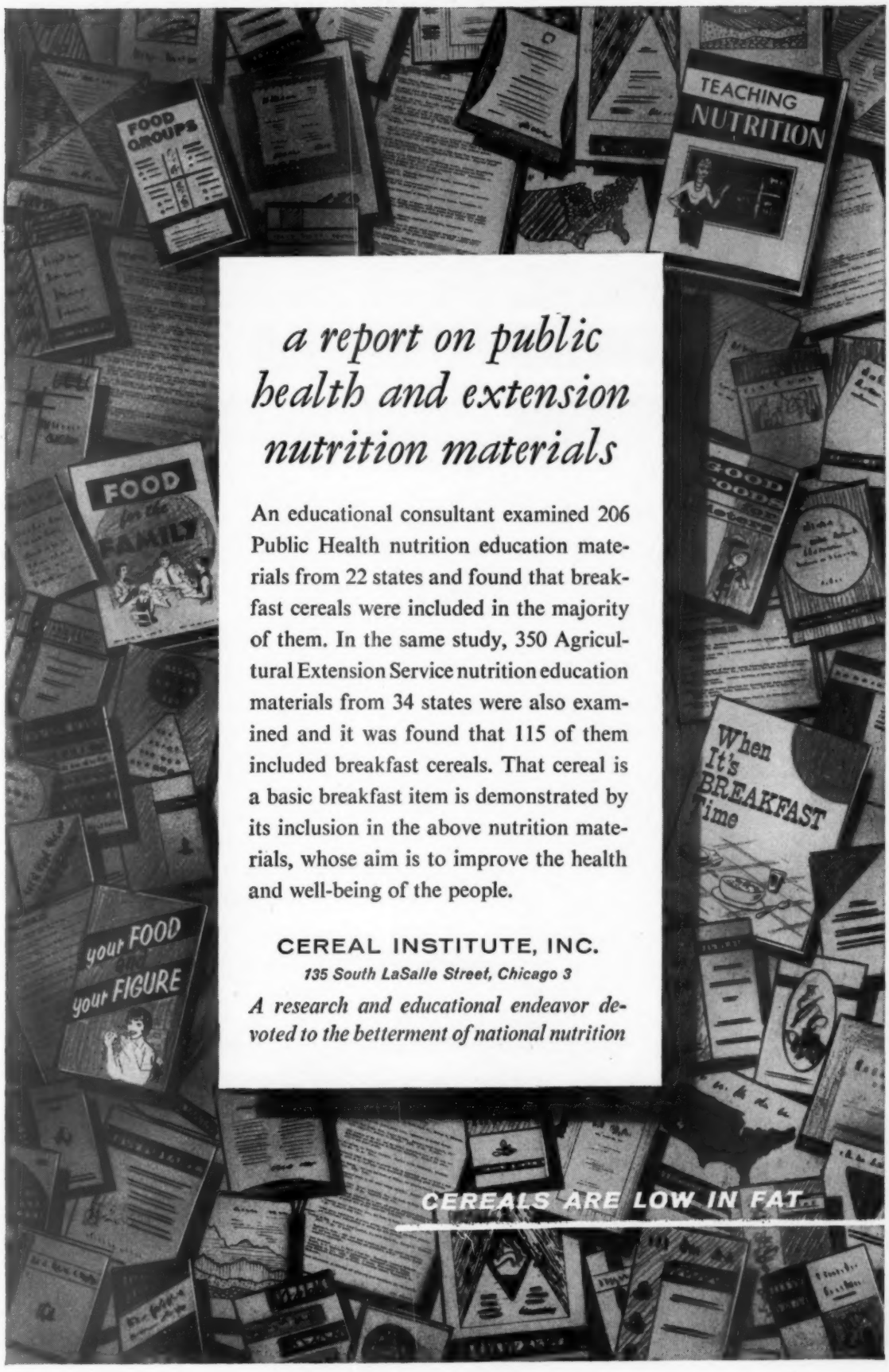

a report on public health and extension nutrition materials

An educational consultant examined 206 Public Health nutrition education materials from 22 states and found that breakfast cereals were included in the majority of them. In the same study, 350 Agricultural Extension Service nutrition education materials from 34 states were also examined and it was found that 115 of them included breakfast cereals. That cereal is a basic breakfast item is demonstrated by its inclusion in the above nutrition materials, whose aim is to improve the health and well-being of the people.

CEREAL INSTITUTE, INC.

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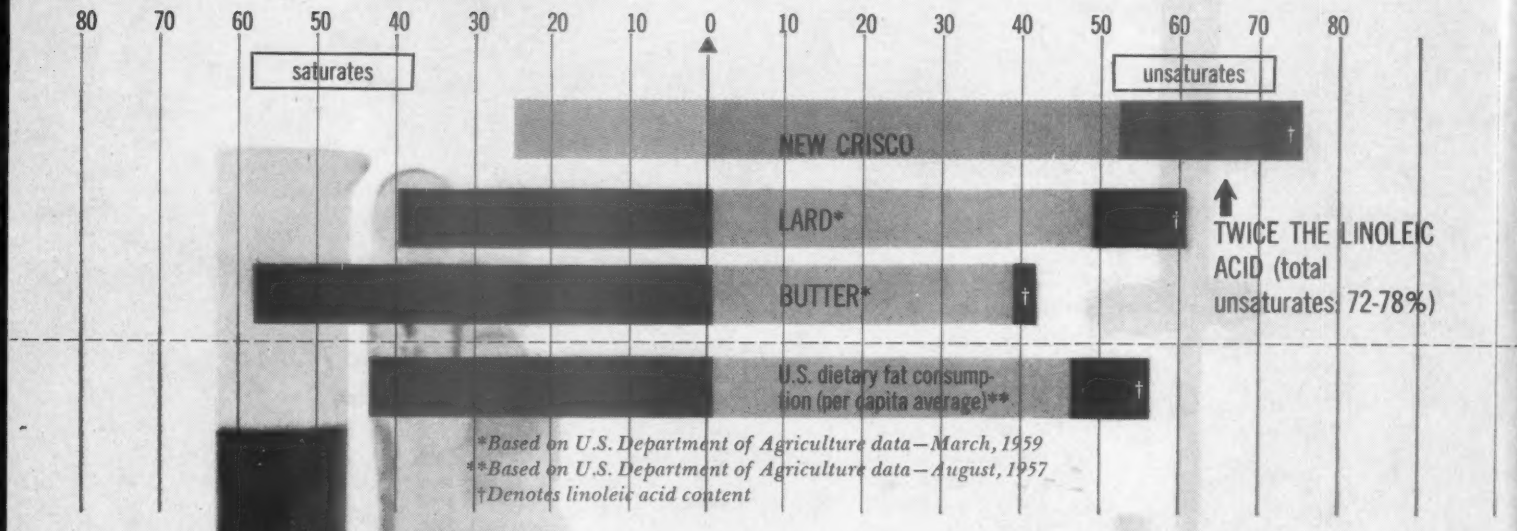
A research and educational endeavor devoted to the betterment of national nutrition

Compare NEW CRISCO'S improved level of preferred lipid factors


80 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80
saturates
unsaturates
NEW CRISCO
LARD*
BUTTER*
U.S. dietary fat consumption (per capita average)**
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TWICE THE LINOLEIC ACID (total unsaturates: 72-78%)

*Based on U.S. Department of Agriculture data—March, 1959
**Based on U.S. Department of Agriculture data—August, 1957
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Your wife can tell you why real shortening is needed for good cooking...

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THE HIGHLY UNSATURATED SHORTENING

doubles the linoleic acid to answer the need for an all-purpose shortening in line with changing views on dietary fat

You, as a physician, know the desirability of adequate sources of linoleic acid even in normal diets. Your wife knows how important shortening is in preparing fine-tasting foods.

Today's prudent diets dictate a more balanced intake of preferred unsaturates—even though a direct causal relationship between dietary fats, serum lipid levels, and cardiovascular diseases is not yet proved.

Helps you prescribe diets patients will follow!

Your patients know the desirability of *real* shortening for all frying and baking because of the wonderful eating characteristics it alone gives to many foods. In fact many of our favorite foods, for example most cakes, cookies, and pastry, can *only* be satisfactorily made with a real shortening, not salad oil. And you know how difficult it is to give up favorite foods—even on doctor's orders.

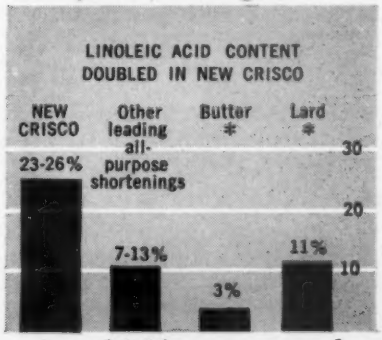
The importance of new Crisco

Hence the importance to you and your patients of new, improved Crisco: A highly unsaturated *vegetable* shortening, new Crisco now provides approximately double the linoleic acid (23-26 per cent) of other leading all-purpose shortenings—and a total of 72-78 per cent unsaturates. In one-half cup of new Crisco there are actually 22 grams of linoleic acid.

For you, this technical achievement means relief from worry about shortenings when patients ask your advice about what are the preferred fats to use. For these patients, use of highly unsaturated new Crisco will permit enjoyment of the advantages of the finest vegetable shortening—yet it also permits them to be on the preferred side dietetically.

Can be recommended with confidence

New Crisco achieves a more favorable level of preferred unsaturates in line with current fat concepts and can be recommended with confidence. Crisco's outstanding *digestibility, performance, appearance,* and *all-purpose versatility* are unchanged.



NEW CRISCO Fatty Acid Composition (Grams/100 Grams)	
Total Unsaturates	72-78
Polyunsaturates. Linoleic	23-26
Others	4-5
Mono-unsaturates	44-50
Total Saturates	22-28
Natural Tocopherols	0.1
Cholesterol	None
Salt (Sodium Chloride)	None

As a highly unsaturated vegetable shortening, with double the linoleic acid content, new Crisco is designed to satisfy not only the needs of the good cook but also the new requirements of the nutrition scientist and physician. 60261

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she wakes refreshed

morning dose controls blood pressure all day

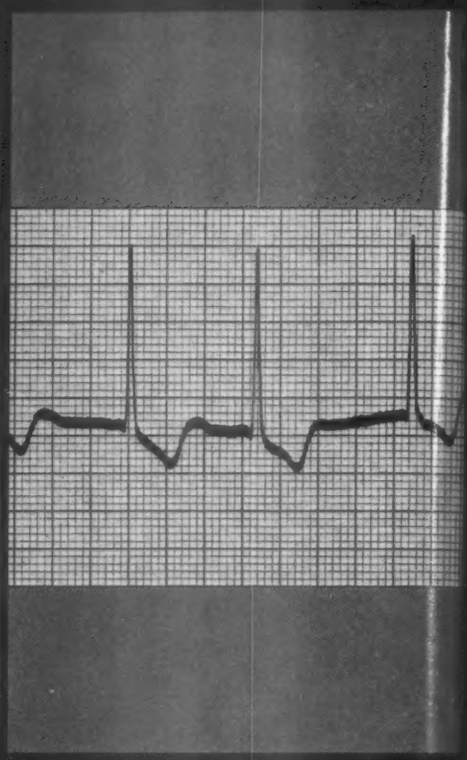
her food tastes better
(thanks to salt liberalization)

edema relieved
(shopping easier)

"cardiac fears" allayed
(zest for life returns)

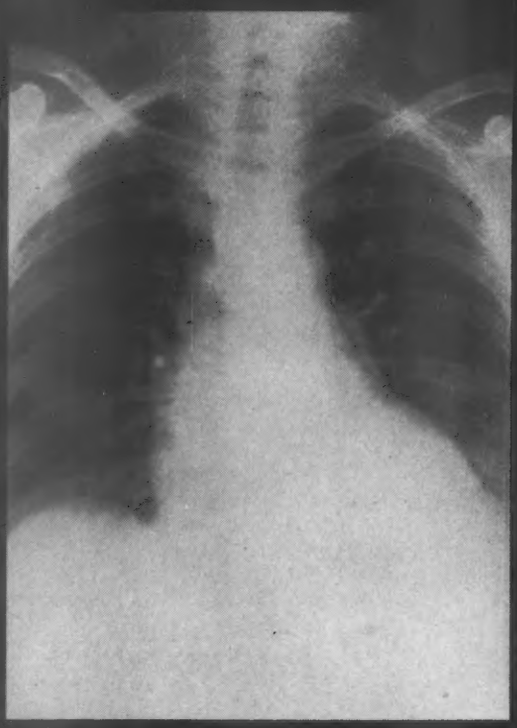
*before treatment**

Cardiac enlargement and pulmonary congestion.

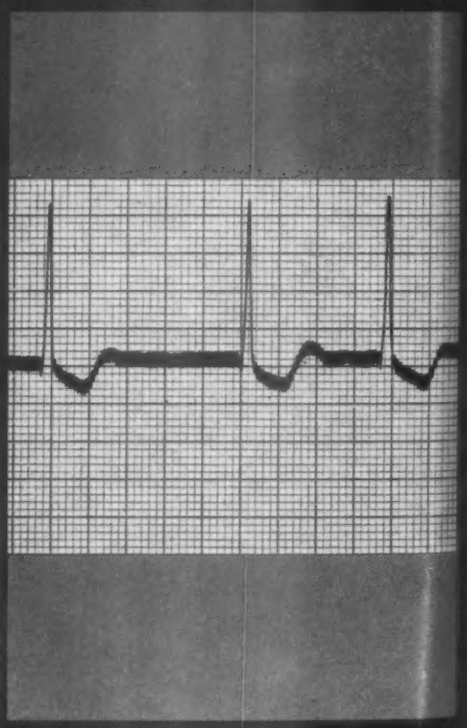


Left ventricular strain and hypertrophy (ST depression in Lead V4).

after one month on HYDROPRES*



Reduction in heart size and clearing of congestion.



Changes toward normal (less ST depression).

*case report

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indicated in all degrees of hypertension

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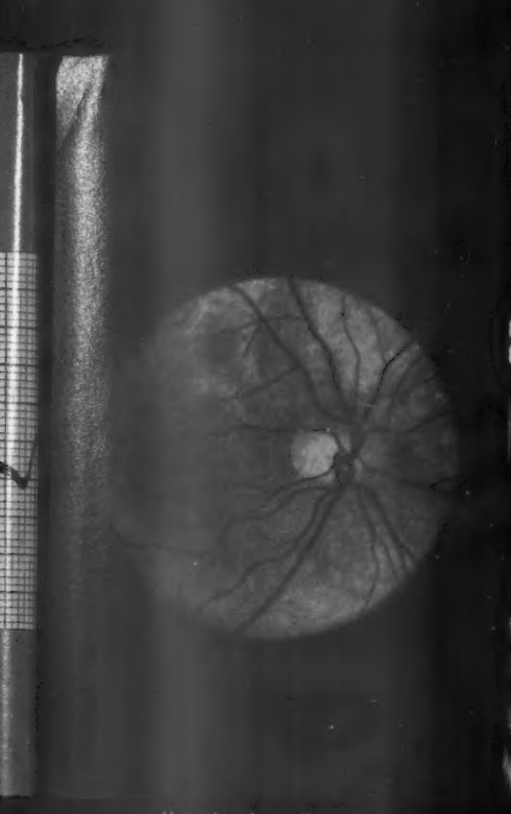
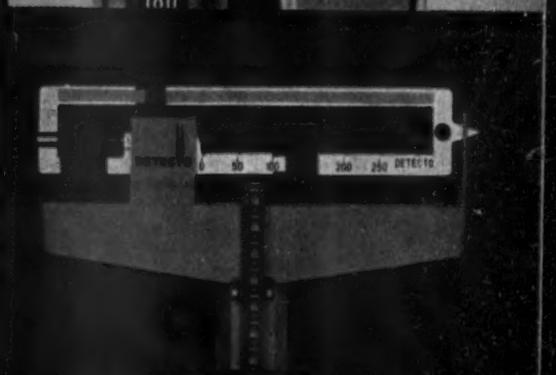
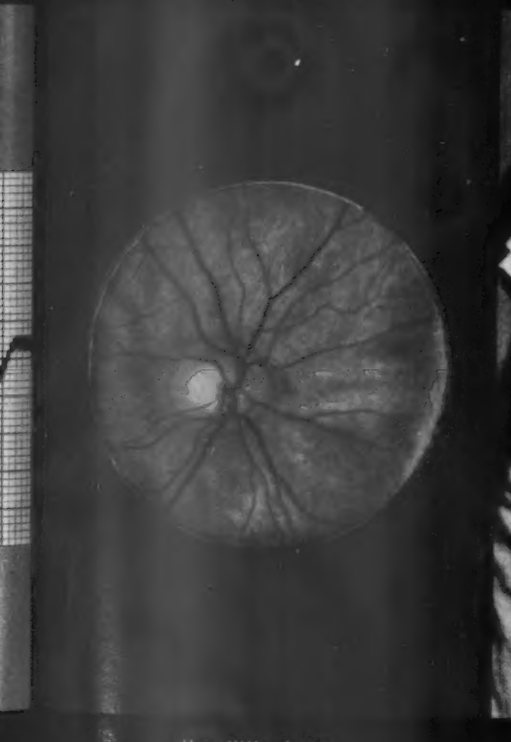


Hypertensive retinopathy with hemorrhages.

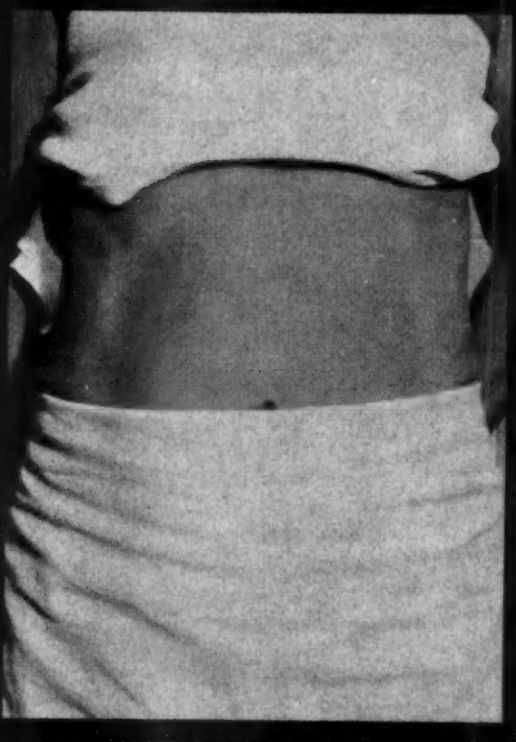
Liver palpable 5 fingerbreadths below costal margin.



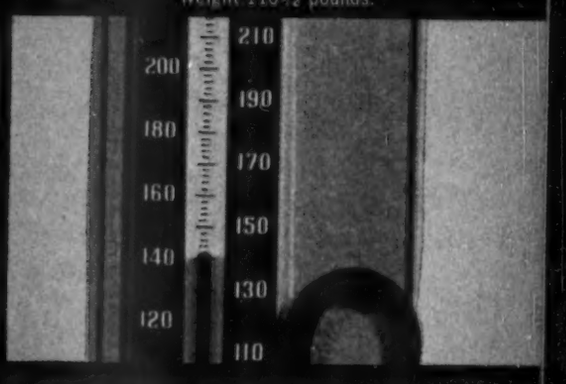
Blood pressure 270/120.
Weight 110½ pounds.

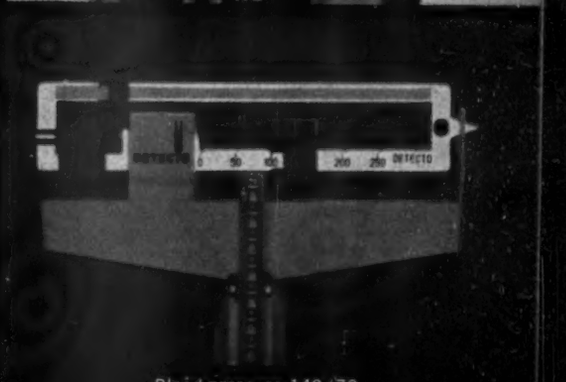


Very little change.



Liver not palpable.





Blood pressure 140/72.
Weight 105 pounds.

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25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to four times a day.

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50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one or two times a day.

also available:

HYDROPRES-Ka†25

25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

HYDROPRES-Ka†50

50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

It is essential to reduce the dosage of other antihypertensive agents, particularly the ganglion blockers, by at least 50 per cent immediately upon addition of these agents or of HYDROPRES Tablets to the regimen.

Before prescribing or administering HYDROPRES, the physician should consult the detailed information on use accompanying the package or available on request.

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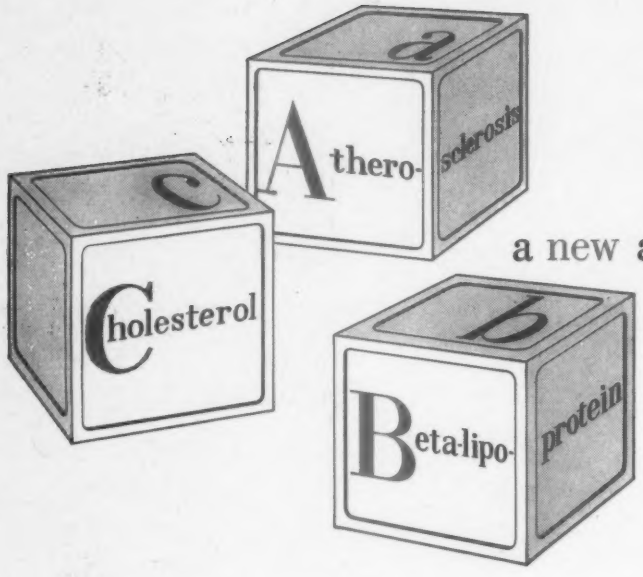

a new approach to these A-B-C's

A recent review of the **atherosclerosis** problem[1] points out that **"cholesterol** is only one of the serum lipids which may be related in some way to atherogenesis" and suggests that "specific triglycerides, phospholipids, fatty acids or the whole spectrum of **beta-lipoproteins** may be of equal or greater importance."

The role of the low-density beta-lipoproteins has been stressed by Olson[2], who suggests that they are the primary agents in atherosclerosis. Another recent discussion[3] has brought out the need for a simple and reliable testing procedure for beta-lipoproteins.

BETA-L TEST® is a specific immunochemical test for estimating serum beta-lipoprotein levels. BETA-L TEST reagent contains antibodies which specifically precipitate the beta-lipoproteins in human sera. This precipitate is then measured visually. Test requires only one drop of patient's serum and can be performed in 10 minutes. Clinical laboratories equipped with a micro-hematocrit centrifuge need no other special equipment for test performance.

In addition to its usefulness in atherosclerotic studies, BETA-L TEST may be found a helpful diagnostic and prognostic procedure in diabetes, hypothyroidism, the menopausal state and other conditions associated with elevated beta-lipoproteins.

BETA-L TEST measurements correlate well with total beta (low-density) lipoprotein measurements obtained by electrophoresis[4] and polyanion precipitation[4] and with cholesterol values in the beta-lipoproteins[5].

BETA-L TEST is supplied in 60-test kits.

1. Goldsmith, G. A.: Highlights on the Cholesterol-Fats, Diets and Atherosclerosis Problem, J.A.M.A. *176:* 783-790 (June 3) 1961.

2. Olson, R. E.: Prevention and Control of Chronic Disease. I. Cardiovascular Disease—with Particular Attention to Atherosclerosis, Amer. J. Public Health *49:* 1120-1128 (Sept.) 1959.

3. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, Am. Pract.-Dig. Treat. *12:* 235-247 (April) 1961.

4. Heiskell, C. L., et al.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222-226 (March) 1961.

5. Bergquist, L. M., Carroll, V. P., Jr., and Searcy, R. L.: Evaluation of a Specific Antiserum for Serum-β-Lipoprotein Estimations, Lancet *i:* 537-538 (March 11) 1961.

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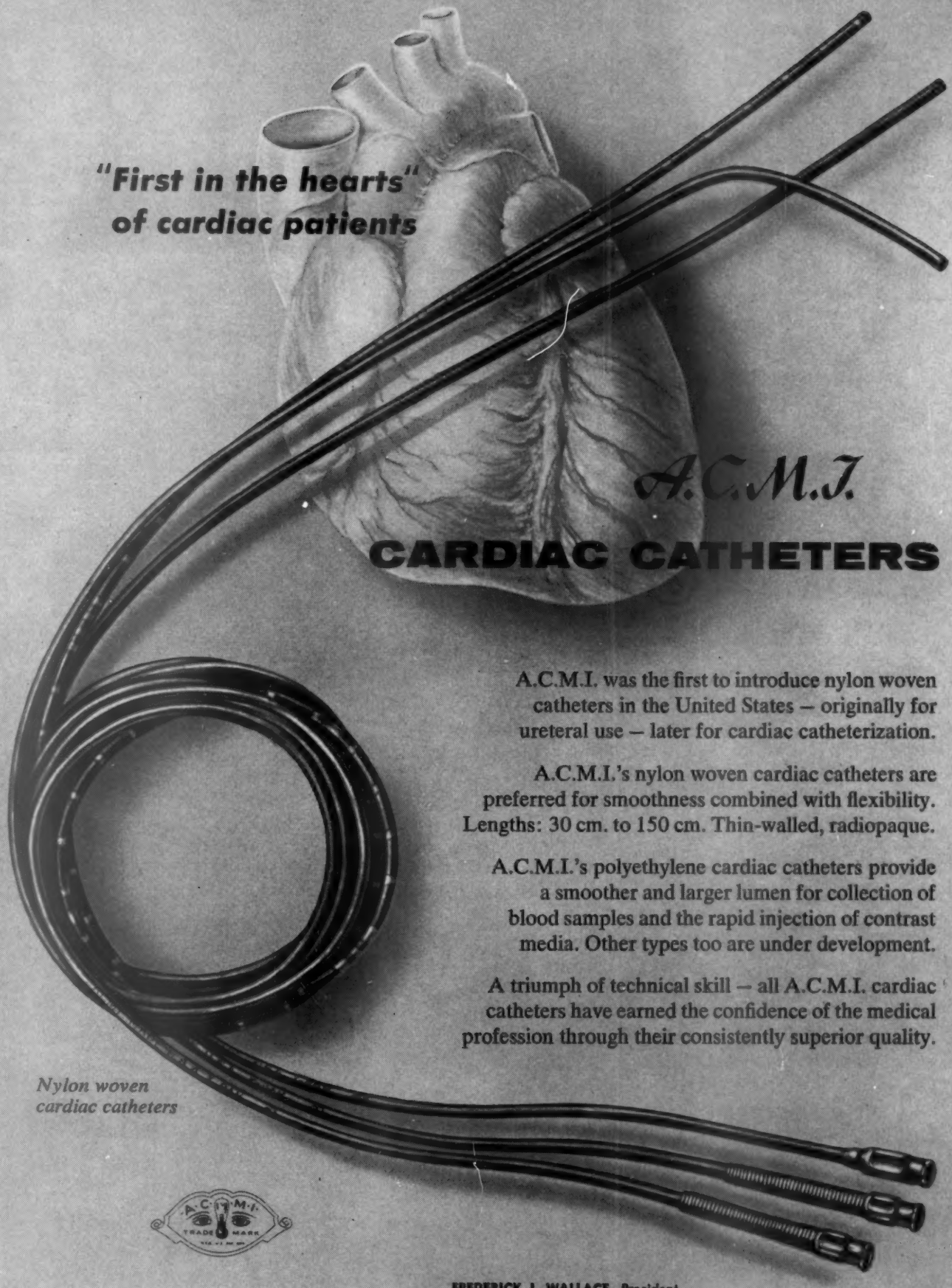

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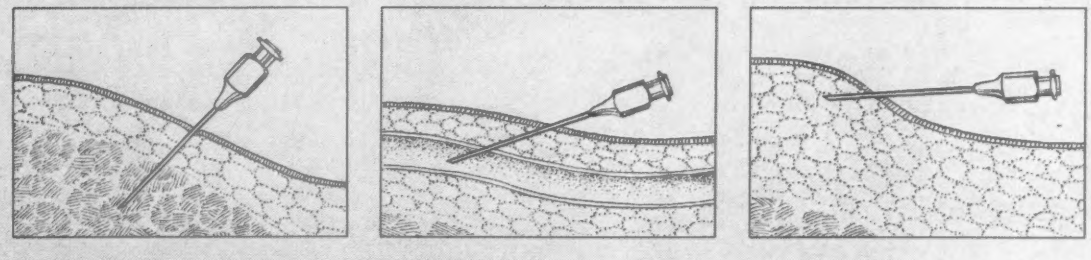

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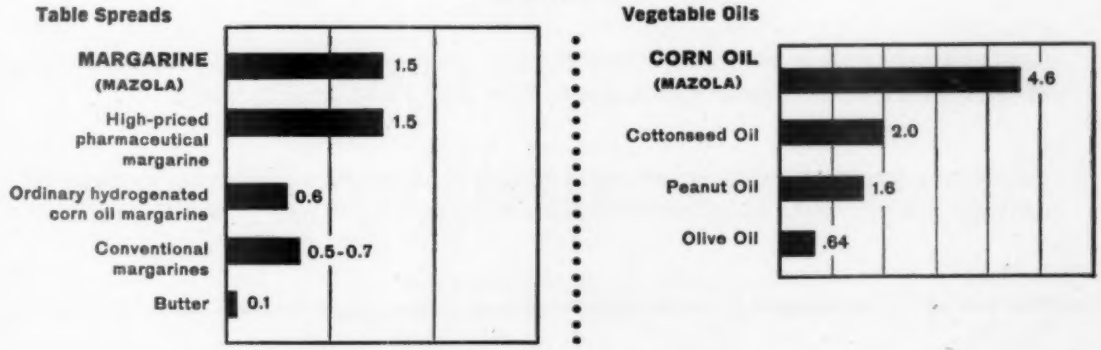

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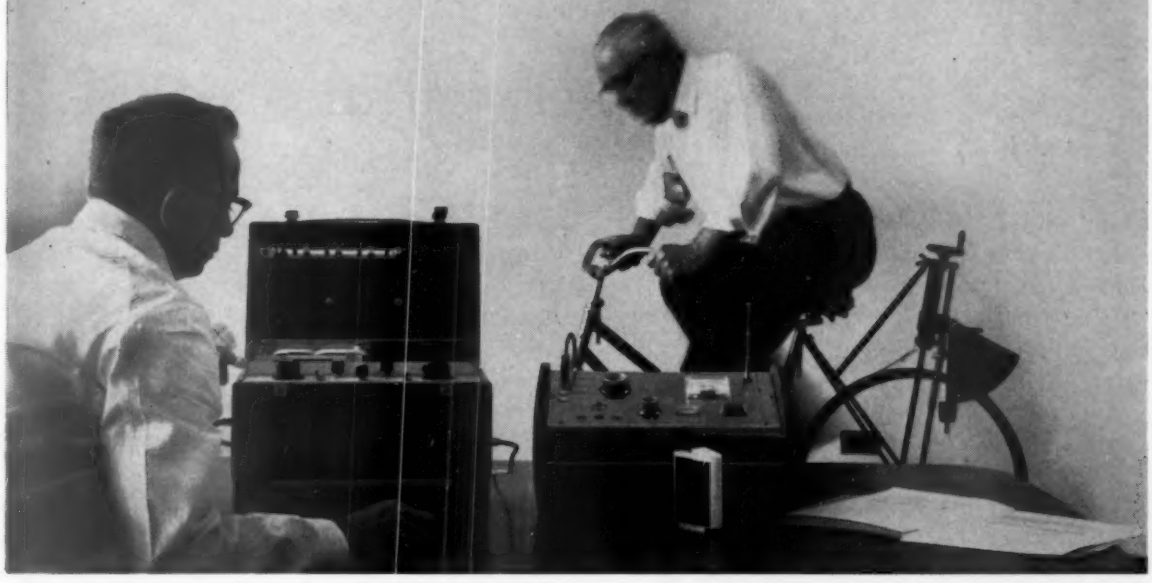
Bellet, S., Deliyiannis, S. and Eliakim, M.: Am. J. Cardiol. *8*:385 (Sept.) 1961



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References: 1. Bellet, S., Deliyiannis, S. and Eliakim, M.: Am. J. Cardiol. *8*:385 (Sept.) 1961. Bellet, S., Deliyiannis, S. and Eliakim, M.: Circulation (in press)

The *RKG 100* system consists of a pocket-size, battery operated radio transmitter worn by the patient; specially designed, Band-Aid type electrodes, and a desk-model receiver which can relay the electrocardiographic waves to conventional recording equipment, an oscilloscope or magnetic tape recorder. The transmitter operates on an authorized radio frequency allocated by the Federal Communications Commission.

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VOLUME VIII NOVEMBER 1961 NUMBER 5

EDITORIAL

Recognizing Compensated Shock

THE CLINICAL PICTURE of noncompensated shock usually is clear cut and readily recognized. However, when compensated or impending shock is present the condition may be difficult to diagnose. A clinician can misinterpret the presence of compensated shock and thus fail to apply early and adequate life-saving treatment.

Recent experiences with a number of patients in a state of compensated shock revealed that they did not receive treatment until it was too late. In each case the attending physician did not initiate proper therapy only because the blood pressure was not at the level commonly and arbitrarily stated for shock. A didactic statement that only a systolic blood pressure reading below 80 mm. Hg is in the shock range may be erroneous in many cases. In the compensated state of shock, homeostatic vasoconstrictor mechanisms spontaneously sustain the pressure from anywhere near normal levels, to hypotensive levels, to an occasional hypertensive level.

Reference to the patient's usual blood pressure level also is necessary. For example, if a patient's normal blood pressure is 180/130 mm. Hg, hypotension may be considered at a pressure of 120/70–60 mm. Hg. If this pressure is allowed to decline further to a level of 80/50 mm. Hg, that patient is, in all probability, in a moribund and preterminal condition.

Physiologic Vascular Adjustments in Shock: In compensated shock, the arterioles of the skeletal muscles, skin, kidneys and gastrointestinal tract constrict to allow the limited circulating blood volume to be shunted to those more vital areas essential for the maintenance of life and least able to withstand ischemia (such as the brain and the heart).[1] If peripheral arteriolar vasoconstriction adjusts the vascular bed to the circulating blood volume, the systemic pressure increases and restores the perfusion pressure of the brain and myocardium (Fig. 1). The patient, although in shock, is in a state of compensated shock. If arteriolar vasoconstriction is insufficient to correct systemic pressure, the patient will remain hypotensive and will then be in a state of noncompensated shock.

When compensatory arteriolar vasospasm of the kidney, gastrointestinal tract, muscles and skin does occur, it can be maintained only for a limited period of time. Because of resultant hypoxemia, the arteriolar musculature becomes paralyzed and secondary vasodilation occurs with peripheral circulatory collapse. Following circulatory collapse, the capillaries of all tissues dilate and the peripheral bed then contains an enormous amount of blood. Thus, there is a further disproportion between the circulating blood volume and the vascular space. The patient now enters a noncompensated phase of shock which usually is an irreversible state. Treatment at this stage is extremely difficult because the vasculature of the target organs is so ischemic and affected by shock-produced vasodepressor substances that it is unable to vasoconstrict.

If vasopressor agents are used when the splanchnic and renal arterioles are trying to compensate, that is, are partially vasoconstricted, physician-induced vasopressor therapy further increases the vasoconstriction of the less vital target organs and the available blood is shunted to the more essential areas.

Treatment: Hypotension in compensated shock caused by cardiac arrhythmias, myocardial in-

[1] CORDAY, E. and WILLIAMS, J. H. Effect of shock and of vasopressor drugs on the regional circulation of the brain, heart, kidney and liver. *Am. J. Med.*, 29: 228, 1960.

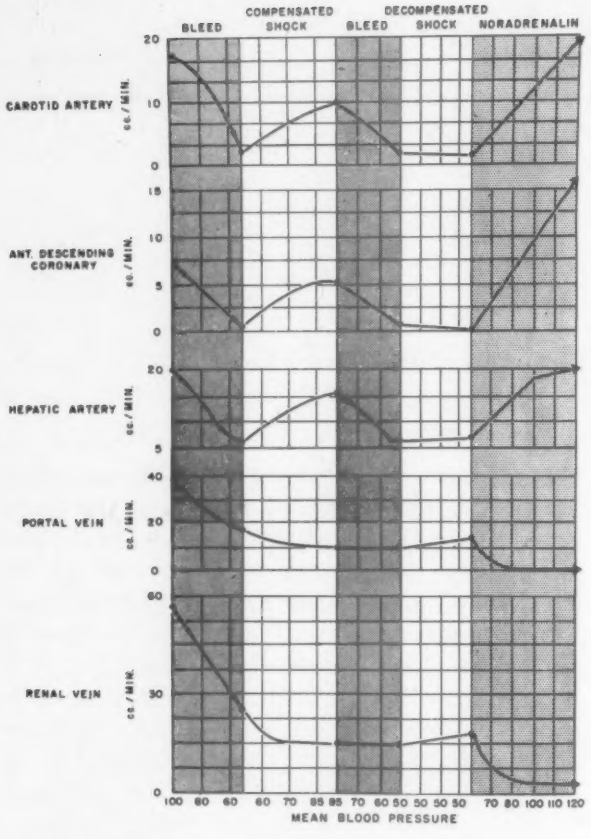

FIG. 1. The effect of bleeding on regional blood flow: A schematic drawing of the regional blood flow of the carotid, coronary and hepatic arteries and the portal and renal veins to demonstrate compensated and noncompensated phases of shock resulting from hemorrhage. After bleeding was stopped the blood pressure rose spontaneously. During the phase of "compensated shock," the carotid flow increased somewhat, the coronary and the hepatic flow increased, but the renal and portal vein blood flow continued to diminish. This demonstrates that the mesenteric and the renal arterioles vasoconstrict in an attempt to restore the systemic blood pressure and return the limited circulating arterial blood flow to the brain, myocardium and liver. With further bleeding, the homeostatic mechanisms which attempt to maintain the systemic blood pressure (the renal, mesenteric and musculoskeletal arterioles) were not able to vasoconstrict further and the blood pressure did not increase spontaneously. A noncompensated state of shock existed. Vasopressor agents increased the blood flow of the carotid, coronary, and hepatic arteries towards normal levels but the circulatory volume of the portal and renal veins diminished somewhat further.

farction or following cerebral vascular thrombosis should be treated promptly with vasopressor agents before the blood pressure declines to excessively low levels. The administration of blood, plasma or plasma expanders is frequently contraindicated because these fluids may overload the vascular circuit. They should be used as replacement therapy only when actual blood loss is present, as in hemorrhage. Vasopressor agents are the treatment of choice for hypotension of both noncompensated and compensated shock.

The signs and symptoms of noncompensated shock are readily recognized; namely, restlessness, weakness, pallor, syncope, oliguria or anuria, cold and clammy skin, absolute hypotension, diaphoresis and loss of skin turgor. The signs of compensated shock are less obvious but because of the underlying physiologic mechanism it is essential that they be recognized. In essence, they also consist of cold and clammy skin, purple mottling of the extremities, pallor, some degree of diaphoresis and a blood pressure reading somewhat lower than normal levels. It is re-emphasized that an arbitrary systolic blood pressure reading of 70, 80 or 90 mm. Hg must not be taken as the sole criterion for shock. For accurate diagnosis of all phases of shock, the blood pressure readings must be considered in combination with all pertinent associated physical signs. A blood pressure reading thought to be within a normal range may be a severe degree of relative hypotension for *that particular subject.*

It is important to understand the clinical picture in its entirety because the physician must anticipate the possible onset of shock in any patient with a recent myocardial infarction, rapid cardiac arrhythmias (especially of ventricular origin) or a cerebral thrombosis. If any patient's history is suggestive of a shock-producing state and if *any* of the signs or symptoms of shock are present, particularly cold, clammy, purple mottled skin and anuria, in all probability the patient is in a state of compensated shock. These patients must be watched closely because they often slip into a decompensated state.

It is wiser to begin vasopressor therapy in a state of compensated shock while the patient is relatively hypotensive and evinces associated signs of cardiac decompensation and arrhythmias, rather than wait for the appearance of dangerous, telltale, markedly hypotensive noncompensated shock. A slight restoration of 20 mm. Hg in the mean blood pressure may increase coronary flow 50 per cent.[2] This may be all that is necessary to correct disturbing

[2] CORDAY, E., WILLIAMS, J. H., DE VERA, L. B. and GOLD, H. Effect of systemic blood pressure and vasopressor drugs on coronary blood flow and the electrocardiogram. *Am. J. Cardiol.*, 3: 626, 1959.

arrhythmias or vicious congestive failure.[3] Prompt therapy of compensated shock is the greatest prophylaxis against life-endangering noncompensated shock.

In summary, because the effectiveness of present day therapy of shock depends on its prompt institution, every effort must be made to recognize the clinical features of the various phases of shock. The recognition of a state of compensated shock might be difficult. Relative hypotension, individually diagnosed for each patient, must be treated as if it were absolute hypotension. Vasopressor therapy is indicated whenever moderate relative hypotension is evident, especially if associated with myocardial infarction, rapid cardiac arrhythmias or cerebral thrombosis.

DAVID W. IRVING, M.D.
ELIOT CORDAY, M.D., F.A.C.C.
Institute for Medical Research
Cedars of Lebanon Hospital
Los Angeles, California

[3] CORDAY, E., GOLD, H., DE VERA, L. B., WILLIAMS, J. H. and FIELDS, J. Effect of the cardiac arrhythmias on the coronary circulation. *Ann. Int. Med.*, 50: 535, 1959.

Clinical Studies

Hypertrophic Subaortic Stenosis

Clinical and Hemodynamic Studies with Special Reference to Pulse Contour Measurement*

GUY M. BOITEAU, M.D. *and* BERTRAM J. ALLENSTEIN, M.D.

Duarte, California

RECENT REPORTS have described hypertrophic subaortic stenosis under multiple terms: pseudoaortic stenosis,[1] obstructive cardiomyopathy,[2] asymmetrical hypertrophy of the heart[3,4] and familial muscular subaortic stenosis.[5] This clinical entity has generated much interest in the last few years because of its similarity to and confusion with aortic stenosis or mitral insufficiency. The surgical treatment of this lesion[6,7] is still in the developmental stage and no valid assessment of the results can yet be made. The diagnosis must be recognized if effective relief for these patients is to be achieved.

It is the purpose of this paper to present the clinical, hemodynamic and angiographic data of three cases of hypertrophic subaortic stenosis and to emphasize specific findings, particularly those related to the pulse contour, which we believe to be of diagnostic value in this condition.

METHODS

Each patient had a fourteen lead electrocardiogram, direct spatial vectorcardiogram (Kimura, Grishman and Frank lead systems), a phonocardiogram and roentgenograms of the chest with barium swallow and cardiac fluoroscopy. *Catheterization data* were obtained as follows: (A) Pressures were recorded by means of a Statham strain gauge, P-23AA, and multichannel photographic recorder. (B) Blood gas analyses were carried out by the method of Van Slyke. Oxygen saturation was determined also by the use of oximeters. (C) Cardiac output was calculated by the Fick principle,[8] and the Stewart[9] and Hamilton[10] methods were utilized when the cardiac output was calculated from indicator dilution curves. (D) Corrected aortic and radial artery upstroke time was calculated from the following formula:

$$\frac{U.T.}{\sqrt{R^1 - R^2}}$$

when U.T. measured upstroke time in the pressure tracing and $R^1 - R^2$ measured interval between peaks of successive R waves in the electrocardiogram.

Selective cardioangiography was performed in two cases in the midleft ventricle through a retrograde aortic catheter.

CASE REPORTS

CASE 1. This was a 40 year old woman with the chief complaints of pain in the chest and palpitations. History of rheumatic fever was denied. At the age of 18 years, on routine examination, a school physician stated that she had a murmur. She married and had five children normally; during her last pregnancy she experienced palpitations for the first time. In October, 1957, when she had "severe pneumonia," she was digitalized. Thereafter she became more aware of cardiac symptoms, and had marked palpitations and retrosternal pain in the chest which radiated to the left shoulder, leaving her left arm heavy and weak. Nitroglycerine relieved the pain in about 2 minutes. The patient was referred to the Center as a case of mitral insufficiency.

Physical examination revealed: peripheral pulses normal in volume; blood pressure in the arm was 120/55 mm. Hg; in the thigh, 130/ 70. Neck veins were not engorged; apex beat thrusting in the fifth intercostal space at the anterior axillary line. A systolic thrill was palpated along the left sternal border at the fifth intercostal space. There was a rough,

* From the Department of Cardiology, Elsinor and George Machris Cardiac Hospital, City of Hope Medical Center, Duarte, California.

ejection type, grade 4, pansystolic murmur between the apex and left sternal border, radiating to the axilla but not to the neck. The second sound at the aortic area was present and equal to the second sound at the pulmonic area. A grade 2 holosystolic murmur was heard at the base, loudest at the aortic area.

Electrocardiogram and vectorcardiogram revealed sinus rhythm, left ventricular hypertrophy, digitalis effect and myocardial ischemia (Fig. 1). The *phonocardiogram* showed a holosystolic murmur with midsystolic accentuation recorded along the left sternal border and at the apex. *Roentgenograms and cardiac fluoroscopy* revealed left ventricular enlargement without significant left atrial bulging. No valve calcification was seen.

Cardiac catheterization (right and left) revealed mild pulmonary hypertension and a systolic gradient of 130 mm. Hg between the left ventricle and infundibular outflow tract of the left ventricle (Table 1). No evidence of aortic or mitral insufficiency was demonstrated by dye dilution curves. The method used here to detect aortic regurgitant flow was demonstrated by Braunwald and Morrow[11] in 1958. No indicator dye was detected at the radial artery or the right ear when dye was injected at various levels in the descending aorta. Also, in order to rule out mitral valvular insufficiency, indicator dye was injected in the midleft ventricle, according to the Marshall technic.[12] No abnormality, such as absence of a systemic recirculation peak or prolongation of the disappearance slope, was demonstrated.

Left heart biplane angiogram showed the left ventricular wall to be thickened with some bowing of the interventricular septum to the left. During systole, there was a very narrow outflow tract approximately 3 to 4 cm. below normal valve cusps. It appeared somewhat tortuous and measured approximately 1 cm. in diameter on the anteroposterior films. There was occasional regurgitation of the opaque media through the mitral valve with varying increase in opacification of the left atrium (Fig. 2).

Case 2. This 37 year old woman's chief complaints were fatigue and dyspnea on exertion. History of rheumatic fever was denied. At age 18, on routine examination, a school physician stated she had a murmur. She had two pregnancies. The last one, in 1954, was complicated by cough, orthopnea and paroxysmal nocturnal dyspnea. In June, 1954, a tooth was extracted without penicillin prophylaxis. Three hours later fever, chills and headache occurred. This continued for 3 weeks. Blood cultures were positive for Streptococcus viridans. The patient responded well to penicillin therapy, but she had fatigue, moderate dyspnea on exertion and occasional paroxysmal nocturnal dyspnea, for which she was digitalized. The complaints have persisted.

Physical examination revealed: blood pressure, 104/50 mm. Hg; neck veins slightly engorged; lungs clear. Point of maximum cardiac impulse was

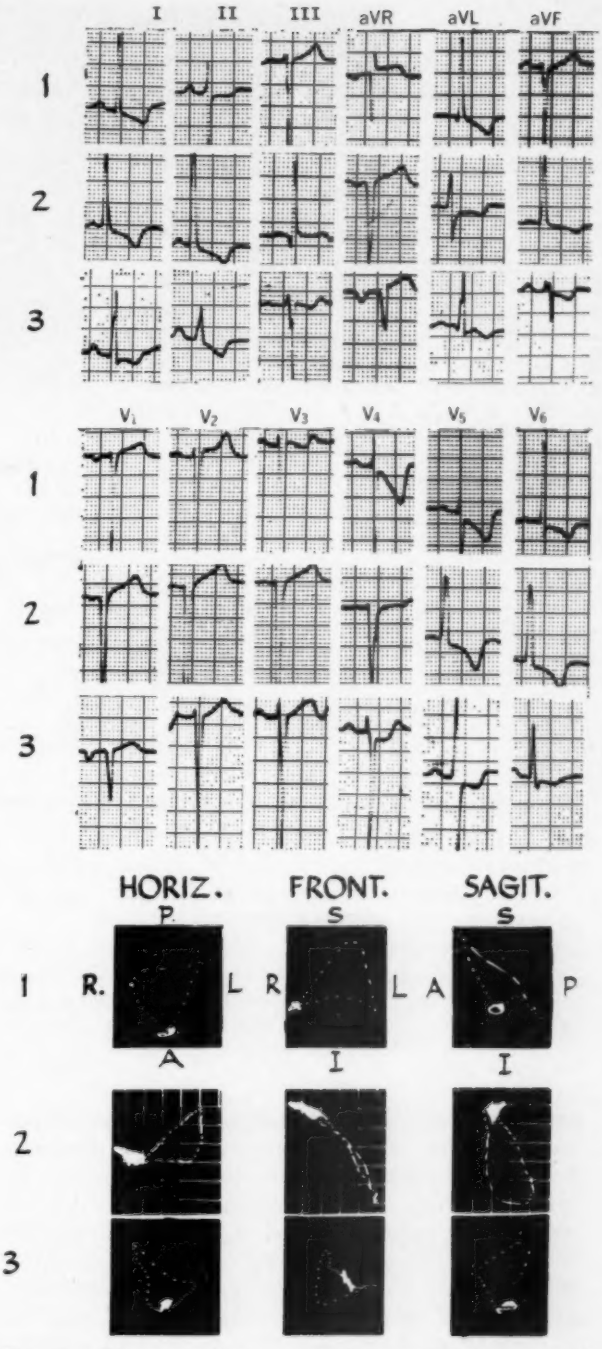

Fig. 1. Electrocardiograms and vectorcardiograms of Cases 1, 2 and 3.

at the sixth intercostal space at the anterior axillary line. Sinus rhythm was present. A systolic thrill was palpated at the apical area. A grade 4, harsh, holosystolic murmur, with midsystolic accentuation, was heard best along the left sternal border at the fifth intercostal space and at the apex, radiating into the axilla. The same murmur was well heard over the precordium, but was less intense at the base and did not radiate well to the carotid areas.

Laboratory data showed hematocrit, 49 per cent;

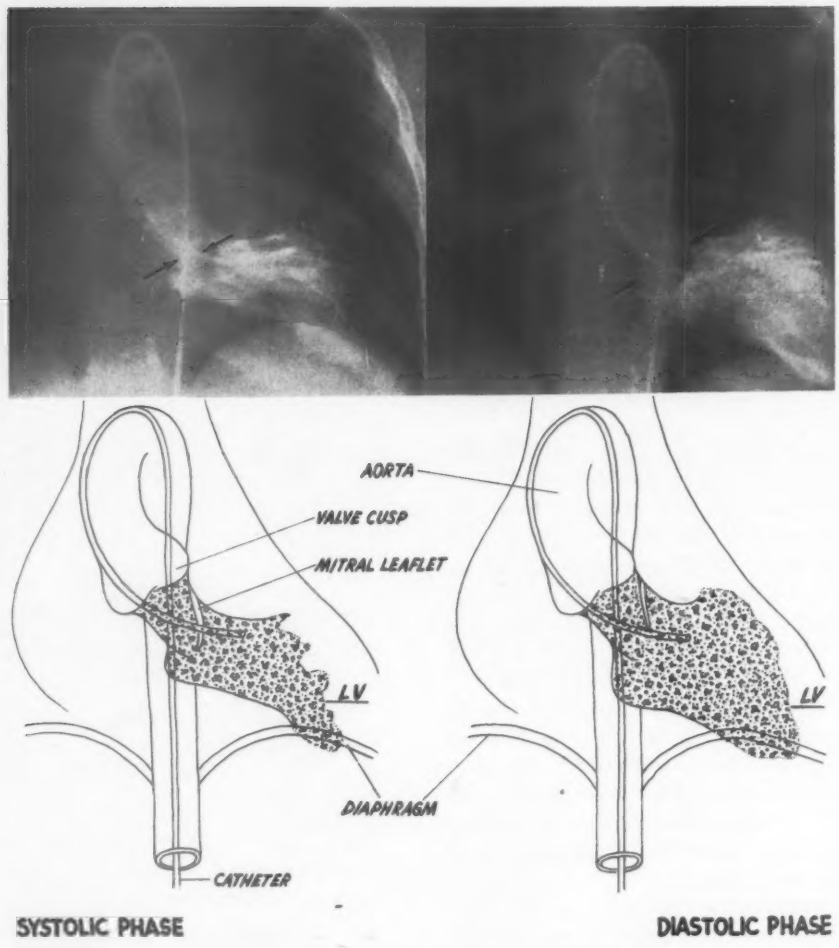

FIG. 2. Case 1. *Left ventriculogram*, anteroposterior films. The narrowing (cone formation) is demonstrated at the outflow tract of the left ventricle in systole by the arrows; the anterior mitral leaflet is well visualized; residual amount of blood in systole is significant.

antistreptolysin O titer, 1:50 units; C-reactive protein, negative; and sedimentation rate (corrected), 5 mm. per hour. *Electrocardiogram* revealed left ventricular hypertrophy and digitalis effect. *Vectorcardiogram* showed abnormal repolarization and left ventricular hypertrophy (Fig. 1). *Phonocardiogram* revealed a holosystolic murmur with midsystolic accentuation at all areas. The second sound was well seen at the aortic area.

Right heart catheterization (March 2, 1959) revealed a long infundibular area at the outflow tract of the right ventricle (systolic gradient 30 mm. Hg). Cardiac index was 2.2 L. per minute per M^2.

Retrograde aortic catheterization, performed on October 27, 1960, demonstrated a long infundibular area at the outflow tract of the left ventricle (systolic gradient of 56 mm. Hg) (Table 1). Dye curves showed no aortic or mitral valve insufficiency.

An *angiogram* done in the midleft ventricle revealed the aortic cusps to be apparently normal. The wall of the left ventricle appeared markedly thickened. The initial filling of the left ventricle outlined an opaque zone around the mitral annulus and showed the interventricular septum to be deviated to the left. There was marked narrowing of the outflow tract of the left ventricle during systole (Fig. 3).

CASE 3. This was a 23 year old woman with chief complaints of fatigability and mild dyspnea on exertion. A heart murmur was first heard at the age of 2 years. Acute glomerulonephritis occurred when the patient was 10 years old. Throughout her adolescent years the only complaints were of some increased fatigability and mild exertional dyspnea, as compared with her classmates. A pregnancy in 1958 was associated with exertional dyspnea, orthopnea and signs of heart failure. Therefore, a therapeutic abortion was performed in December 1958. A diagnosis of subacute bacterial endocarditis was made and confirmed by blood culture (Streptococcus viridans). She had a good response to penicillin therapy.

Physical examination revealed peripheral pulses with good volume; blood pressure was 112/80 mm.

TABLE 1
Hemodynamic Findings in Three Cases of Hypertrophic Subaortic Stenosis

Case No.	Pressures (mm. Hg)					Ejection Time (sec.)		Corrected Upstroke Time (sec.)		Maximum Velocity (mm. Hg/sec.)		Cardiac Output (L./min.)	Cardiac Index (L./min./M²)
	Central Aorta	Radial Artery	Left Ventricle	Infundibulum	Systolic Gradient*	Central Aorta	Radial Artery	Central Aorta	Radial Artery	Central Aorta	Radial Artery		
1	90/55	92/50	220/12–18	90/12–15	130	0.36	0.36	0.06	0.06	775	775	3.5	2.2
2	104/62	120/65	160/5–20	104/5–25	56	0.35	0.35	0.06	0.06	1140	1140	3.6	2.5
3	93/60	110/50	255/7–12	...	162	0.38	0.37	0.31	0.17	220	860	8.8	5.4
Prior to surgery	110/85	116/70	240/35–55	140/45–60	100	...	...	...	...	...	...	...	...
After surgery	120/60	110/60	250/10–25	...	130	0.40	0.42	0.10	0.12	560	560	...	...

* Systolic gradient between midleft ventricle and infundibular zone of left ventricle.

Hg. There was no neck vein engorgement. The maximum apical impulse was palpated in the fifth intercostal space at the anterior axillary line. A systolic thrill was palpable over the entire precordium and suprasternal notch. The second sound at the aortic area was present. There was a grade 4, rough, systolic murmur with midsystolic accentuation heard at the second right and left intercostal spaces. It radiated into the neck, left sternal border, apex, and to the back in the left paraspinous areas. No diastolic murmur was present.

Chest fluoroscopy revealed some cardiac enlargement with primary left ventricular predominance. No valvular calcification was visible. The *electrocardiogram* showed sinus rhythm, normal QRS axis, intermediate heart position and left ventricular hypertrophy. The *vectorcardiogram* revealed left ventricular hypertrophy.

Left heart catheterization by the Brock technic[13] revealed a systolic gradient of 162 mm. Hg between the ascending aorta and left ventricle (Table 1). The radial artery corrected upstroke time was within normal limits. The cardiac index was 5.4 L. per minute per M².

Open heart surgery was performed on March 18, 1960. Pressures were taken prior to cardiotomy. There was a pressure gradient of 100 mm. Hg between the outflow tract of the left ventricle and the midleft ventricle. At operation the valve cusps were small but appeared normal. A subaortic fibrous ring was thought to be felt and was resected, but a pressure gradient persisted (Table 1). The heart was bypassed a second time and muscular hypertrophy at the left ventricular infundibulum was suspected. However, the patient's condition became worse. Frothy sputum was seen in the intratracheal tube and the patient died.

At autopsy, the aortic valve cusps appeared slightly thickened but otherwise normal. A remnant of a subaortic fibrous ring was noted, but the muscular portion of the outflow tract of the left ventricle was thickened. The entire left ventricle was hypertrophied. No significant mitral valve obstruction or regurgitation was found, but the mitral valve was thickened, apparently due to healed bacterial endocarditis.

HEMODYNAMIC DATA

The pertinent hemodynamic data are summarized in Table 1. In our three cases, central aortic and radial artery upstroke time was rapid, ranging from 0.06 to 0.10 second (normal, 0.10 to 0.16 second).[14] The slopes of the ascending limbs of the central aorta and radial artery pressures rose parallel to each other. The upstroke slope of the left ventricle and ascending aorta were actually coincident in Case 3 following incision of the subaortic ring.

The total ejection time in both central aorta and radial artery was prolonged, ranging from 0.35 to 0.41 second, compared to the normal range of 0.28 to 0.31 second.[15] A double systolic wave was seen in the central aorta and peripheral artery pressure curves. The first wave

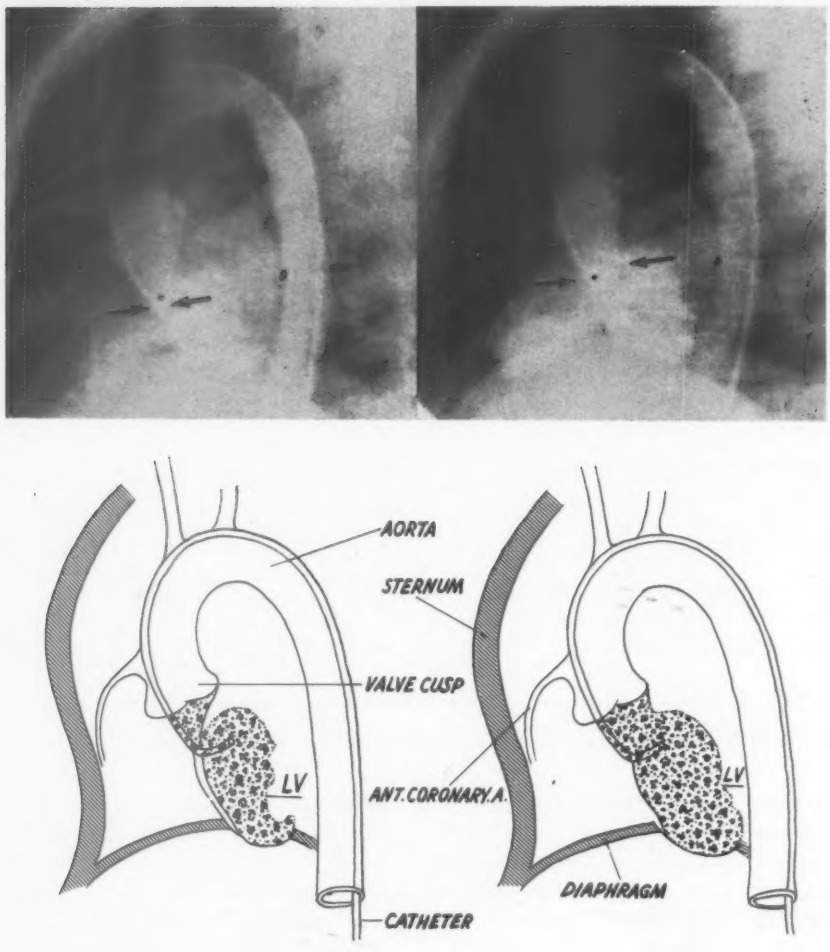

FIG. 3. Case 2. *Left ventriculograms*, lateral films. The opacification within the left ventricle demonstrated the narrowing (cone formation) in systole at the outflow tract. Arrows indicate the areas involved. Valve cusps appear normal. There is also a pectus excavatum present.

was steep and synchronous with the left ventricular ascending limb. The second wave was lower and smoother in contour.

A withdrawal tracing from the midleft ventricle to the ascending aorta showed a long infundibular zone and a systolic pressure gradient varying from 56 to 162 mm. Hg between the left ventricular cavity and infundibulum. Prior to open heart surgery in Case 3, there was a mild systolic and diastolic pressure gradient between the left ventricular outflow tract and ascending aorta.

The radial artery double systolic peak was not simultaneous with central aortic peaks but followed the central aortic curve in a similar fashion. Both central and radial artery curves were similar. Maximum velocity (steepest portion of the upstroke) was the same in the central aorta and radial artery tracings in Cases 1 and 2. The normal value in the peripheral artery[14] is 750 to 1250 mm. Hg per second; in the central aorta[16] we have found the normal to be 350 to 750 mm. Hg per second. In Case 3, before incision of the subaortic ring, the maximum velocity was 220 mm. Hg per second in the ascending aorta, and 860 mm. Hg per second in the radial artery. After surgery the maximum velocity was the same in both areas: 560 mm. Hg per second (Fig. 4).

The resting cardiac index was slightly below the normal range in Cases 1 and 2 and increased in Case 3. The end-diastolic pressure in the midleft ventricle was elevated although there was no clinical evidence of congestive heart failure.

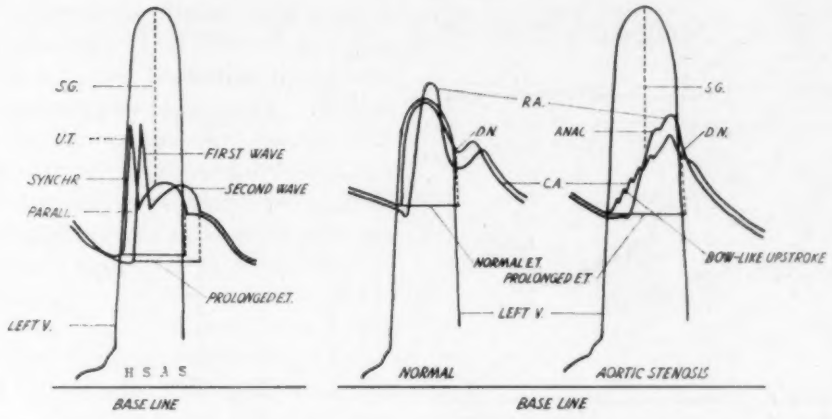

FIG. 4. *Comparison between simultaneously recorded pulses in left ventricle, central aorta and radial artery in subaortic and aortic stenosis.* HSAS = hypertrophic subaortic stenosis; S.G. = systolic gradient; U.T. = upstroke time (rapid); E.T. = ejection time; Lt. V. = left ventricle; D.N. = dicrotic notch; R.A. = radial artery; C.A. = central aorta; Synchr. = synchronism between the central aorta and left ventricular upstroke; Parall. = parallelism between the central aorta and radial artery upstroke; first wave: due to high flow velocity in early systole, early emptying of the infundibulum; second wave: due to muscular obstruction; late activation of the outflow tract hypertrophy of left ventricle.

COMMENTS

CLINICAL FEATURES

We have described three cases of hypertrophic subaortic stenosis. The clinical characteristics of this disease are as follows: A systolic thrill is palpable at the fifth left intercostal space; the aortic sound is normal; there is a harsh, holosystolic murmur with midsystolic accentuation. It is maximal inside the apex near the fifth left intercostal space. The same murmur, but with less intensity, can be heard along the left sternal border, over the precordium, and at the aortic area; it may or may not radiate well into the neck. In Case 3, however, in which there was also a subaortic fibrous ring, the murmur radiated well into the neck.

The electrocardiogram and vectorcardiogram reveal left ventricular hypertrophy with inverted T waves and depressed S-T segments. The roentgenograms of the chest and fluoroscopy demonstrate cardiac enlargement due to an increased left ventricular mass. *No intracardiac calcification* is visible.

HEMODYNAMIC FINDINGS

Normally the pulse contour of the central aorta is similar to the left ventricular contour and has an inverted U-shaped appearance. The corrected upstroke time in patients with normal aortic valves[16] is 0.18 to 0.24 second in the ascending aorta. There are changes in both time and contour, as the arterial pulse proceeds to the periphery. The radial or brachial pulse exhibits a more rapid ascent to a later or simultaneous and yet higher peak. The normal peripheral pulse contour reveals a more rapid upstroke time than in the central aorta. The normal range in the radial artery is 0.10 to 0.16 second.[14] Therefore, if both pulses mentioned are simultaneously recorded, one sees some difference in their arterial upstroke time and slope (Fig. 4).

In our cases of hypertrophic subaortic stenosis, the hemodynamic aspects were quite unusual. The following characteristics were noted.

Rapid Upstroke Time: In contrast with the normal curves just mentioned, the upstroke slope rose very quickly in both the central aorta and radial artery, demonstrating an early ejection of blood at the opening of the aortic valve. The following mechanism is suggested. We know by experimental electrocardiography that the outflow tract of the left ventricle is the last portion of the left ventricle to be depolarized.[17] In hypertrophic subaortic stenosis, the muscular portion of the outflow tract is hypertrophied and is the last part of the ventricle to be activated. During early systole there is early emptying of the infundibulum, and the flow of blood is ejected with high velocity, but the subaortic muscular portion intervenes promptly to block the ejection of blood and

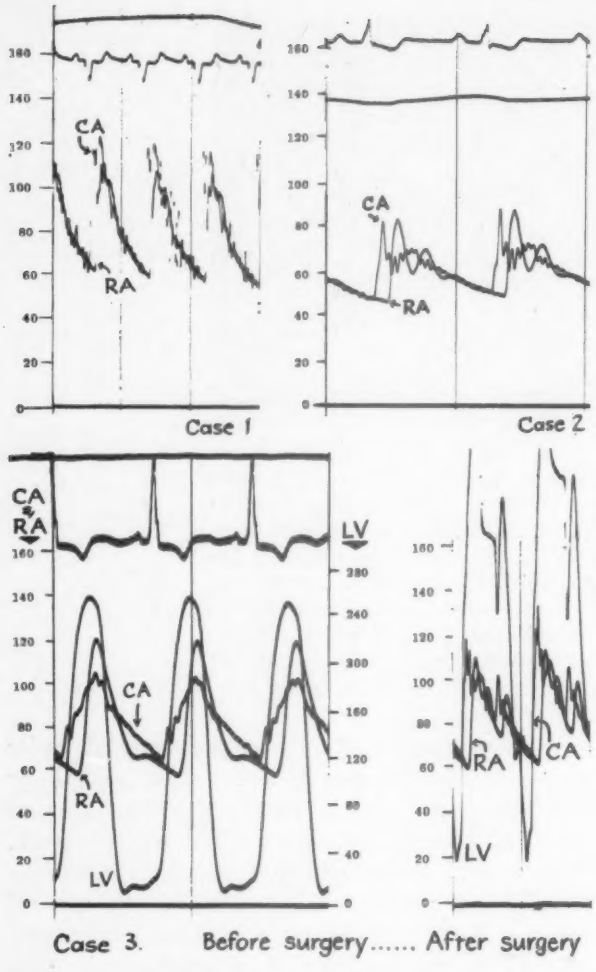

FIG. 5. *Arterial pulse contour in three cases of hypertrophic subaortic stenosis.* Note the rapid upstroke time, the parallelism between the central aorta (CA) and radial artery (RA) ascent in Cases 1 and 2 and the synchronism between the central aorta and left ventricular (LV) upstroke in Case 3, *after surgery.*

leaves a significant residual amount of blood in the ventricle. This can be demonstrated during the ventricular angiograms (Figs. 2 and 3).

This mechanism would also explain the very interesting finding of two systolic waves; one in early systole and the other produced during late contraction of the outflow tract of the left ventricle. The double systolic wave is certainly unique in the field of pulse contour and probably, by itself, represents a diagnostic feature of subaortic stenosis (Fig. 4).

The muscular obstruction is formed by a hypertrophied ventricular septum and a thick muscular wall at the outflow tract of the left ventricle. This builds a narrow and tortuous channel which can be demonstrated during left ventricular angiography (Figs. 2 and 3). In comparison, when aortic valve stenosis is present, the ejection of blood is forced out into the aorta in a turbulent way, through a fixed small orifice. Thus, a slow upstroke is produced, and the tighter the aortic orifice, the longer the upstroke slope. The aortic systolic peak is single, occurring later in systole, and is often simultaneous with the peripheral arterial peak.

Synchronism between Left Ventricular and Central Aortic Curve: As demonstrated by Soulié,[18] the aortic pressure curve rises as soon as the valve opens synchronously with the ventricular upstroke (Fig. 5). The radial artery pulse also rises quickly, parallel to the aortic pulse. In contrast, in aortic valvular stenosis, the aortic curve angles sharply in a slow stroke to form an inverted V-shape.

There was a marked change in pulse contour prior to and after separation of a subvalvular ring (Case 3). The demonstration of the inverted V-shape central aorta pulse *before*, the synchronism among the upstroke times of the simultaneously recorded left ventricle, central aorta and radial artery pulses *after* incising the ring but without relieving the muscular hypertrophy, was further indication of the specificity of pulse configuration in the entity under discussion (Fig. 5).

Johnson[19] mentioned concerning functional infundibular pulmonic stenosis of the contractile type that "the infundibular wave will coincide with the right ventricular at the start of its upstroke, but the infundibular diastolic descent will overlap that of the right ventricle by about 0.1 second." The same parameters are applied to the left side of the heart. We have noted in Cases 1 and 2 that the infundibular contraction which will result in complete occlusion between the left ventricle and infundibulum commences 0.10 and 0.12 second, respectively, after that of the left ventricle activation. The infundibular contraction corresponds to the second systolic wave in the central aortic pulse (Fig. 4).

Prolonged Ejection Time: Due to later contraction of the hypertrophied muscle, there is a double systolic wave. An ejection time of 0.35 to 0.42 second in the central aorta and peripheral artery is certainly prolonged compared with the normal of 0.28 to 0.31 second.[15] Benchimol et al.,[20] using indirect arterial studies, have mentioned two cases of muscular subaortic stenosis in which the total ejection time was prolonged and there was a quick rising pulse. In our direct simultaneous recordings

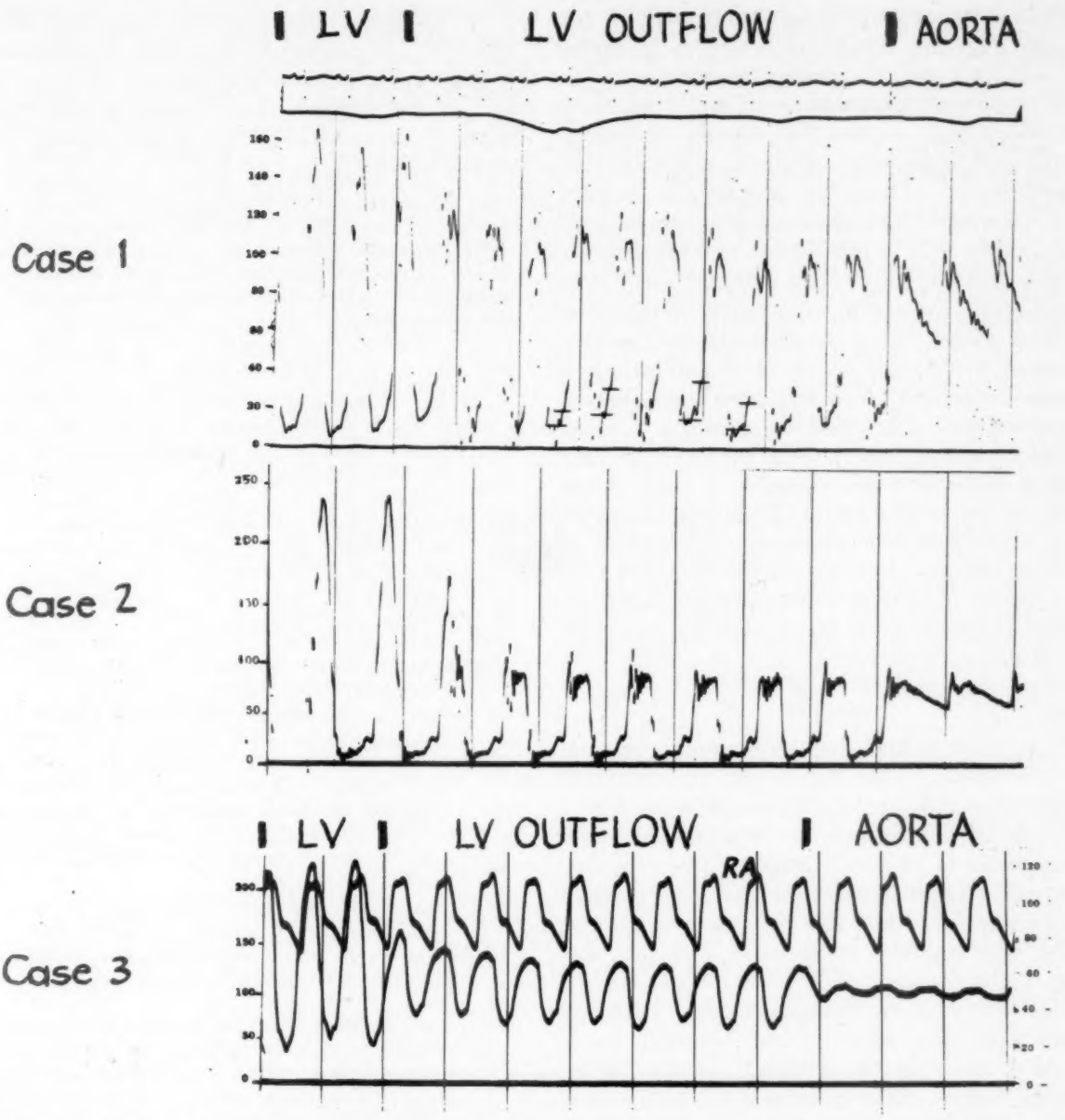

FIG. 6. *Withdrawal tracings* during retrograde left heart catheterization in hypertrophic subaortic stenosis in Cases 1, 2 and in Case 3, which was also associated with a subaortic ring. In the latter case, there is also a mild systolic gradient across the aortic valve, due to the subaortic ring.

of central aorta and peripheral artery, we are in agreement with their findings of prolonged total ejection time, but we have not found a well-defined incisural dicrotic wave.

Repercussion-like Wave: Alexander,[21] in animal experimentation, has demonstrated that the standing wave oscillation (major wave being the dicrotic) is reproduced at the same time in the central aorta and peripheral artery. In our cases of hypertrophic subaortic stenosis, it is to be noted that the peripheral oscillation wave occurs after the aortic, and the whole peripheral artery curve seems to be a repetition of the central aortic pulse. Hence the term "repercussion-like" wave is used.

Premature Ventricular Contraction Phenomenon: We have observed in our cases the "premature ventricular contraction phenomenon," as mentioned by Brockenbrough.[22] The beats following premature ventricular contractions always exhibited lower arterial pulse pressure than did the normal beats, i.e., arterial pulse pressure varied inversely with left ventricular systolic pressure and with the duration of systole.

Infundibular Area: During retrograde aortic catheterization, one may demonstrate the in-

fundibular stenosis nicely by withdrawal of the catheter from the midleft ventricle to the aorta (Fig. 6). One may also demonstrate the approximate length of the infundibulum by taking a spot x-ray film as soon as systolic pressures change and again when diastolic pressures rise to aortic level. Thus, one may be able to estimate the length in centimeters of the hypertrophic area. It is interesting to note that in Cases 1 and 2 a No. 8 NIH catheter was easily passed across the aortic valve many times without significant difficulty. This is not usually as easily performed in aortic valve stenosis.

Angiocardiography: The angiocardiogram done by retrograde catheterization shows a normal valvular contour, a very thick left ventricle and marked reduction of opacifying dye *during systole*, at the outflow tract of the left ventricle. Thus, there is a cone formation followed by a tortuous narrow channel (which is about 3 to 4 cm. below the valve) which disappears during diastole (Figs. 2 and 3) and reappears with each ventricular contraction.

Summary

Three cases of hypertrophic subaortic stenosis are presented. The following clinical and hemodynamic characteristics are demonstrated:

1. A diamond-shaped holosystolic murmur was present at the fifth left intercostal space, inside the cardiac apex; the aortic second sound was well heard. The murmur was less intense at the base and not transmitted well into the neck.

2. There was synchronism of the rapid upstroke time and slope of the simultaneously recorded left ventricular and central aortic pressure curves. Also present was a parallelism of the radial artery upstroke time with that of the central aortic pressure curve. A prolonged ejection time was seen and a large secondary systolic wave, representing the subaortic muscular obstruction, was noted.

3. It is our belief that the unusual central and peripheral arterial pulse contour in hypertrophic subaortic stenosis represents, by itself, a diagnostic feature of this disease if not complicated by other anomalies.

4. The beats following premature ventricular contractions always exhibited lower arterial pulse pressure than did the normal beats.

5. Angiocardiography showed a cone formation and marked diminution of the outflow tract lumen during systole, about 3 cm. below the valve, and normal contour of the valvular cusps.

6. Of special interest is that two of the three patients had subacute bacterial endocarditis, responding to penicillin therapy.

7. One patient died following attempted surgical correction of the hypertrophic subaortic stenosis.

Acknowledgment

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References

1. Bercu, B. A., Dietert, G. A., Danforth, W. H., Pund, E. E., Jr., Ahlvin, R. C. and Belliveau, R. R. Pseudoaortic stenosis produced by ventricular hypertrophy. *Am. J. Med.*, 25: 814, 1958.
2. Goodwin, J. F., Hollman, A., Cleland, W. P. and Teare, D. Obstructive cardiomyopathy simulating aortic stenosis. *Brit. Heart J.*, 22: 403, 1960.
3. Hollman, A., Goodwin, J. F., Teare, D. and Renwick, J. W. A family with obstructive cardiomyopathy (asymmetric hypertrophy). *Brit. Heart J.*, 22: 449, 1960.
4. Teare, D. Asymmetrical hypertrophy of the heart in young adults. *Brit. Heart J.*, 20: 1, 1958.
5. Brent L. B., Aburand, A., Fisher, D. L., Moral, T. J., Myers, J. D. and Taylor, W. J. Familial muscular sub-aortic stenosis: an unrecognized form of "idiopathic heart disease" with clinical and autopsy observations. *Circulation*, 21: 167, 1960.
6. Brock, R. B. Functional obstruction of the left ventricle. *Guy's Hosp. Rep.*, 106: 391, 1956.
7. Brock, R. B. and Fleming, P. R. Aortic subvalvular stenosis. *Guy's Hosp. Rep.*, 105: 391, 1956.
8. Hamilton W. F. Studies on circulation; further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions. *Am. J. Physiol.*, 99: 534, 1932.
9. Stewart, G. N. Researches on the circulation time and on the influences which affect it. *J. Physiol.*, 22: 159, 1897.
10. Fick, A. Über die Messung des Blut Quantums in den Herzventrikeln. Cited by: Hoff, H. E. and Scott, H. J. Physiology (continued). *New England J. Med.*, 239: 120, 1948.
11. Braunwald, E. and Morrow, A. G. A method for the detection and estimation of aortic regurgitant flow in man. *Circulation*, 17: 505, 1958.
12. Marshall, H. W., Connolly, D. C. and Wood, E. H. Physiologic considerations in the selection of patients for mitral commissurotomy. *Med. Clin. North America*, July, p. 1065, 1958.
13. Brock, R., Milstein, B. B. and Ross, D. N. Percutaneous left ventricular puncture in the assessment of aortic stenosis. *Thorax*, 11: 163, 1956.
14. Wood, P. Aortic stenosis. *Am. J. Cardiol.*, 1: 553, 1958.

15. KROEKER, E. J. and WOOD, E. H. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. *Circulation Res.*, 3: 623, 1955.
16. Unpublished data.
17. BARBATO, E., FUJIOKA, T., CARLOS-DEBES, A., PILEGGI, F., FILHO, C. B., SILVA, P. P. and DECOURT, L. V. Study of the sequence of ventricular activation and the QRS complex of the pathologic human heart, using direct epicardial leads. *Am. Heart J.*, 56: 340, 1958.
18. SOULIÉ, P., DEGEORGES, M., JOLY, F., CARAMANIAN, M. and CARLOTTI, J. Une cause d'erreur dans le diagnostic hemodynamique des retrecissements aortiques. *Arch. mal. coeur*, 52: 1022, 1959.
19. JOHNSON, A. M. Functional infundibular stenosis: its differentiation from structural stenosis and its importance in atrial septal defect. *Guy's Hosp. Rep.*, 108: 373, 1959.
20. BENCHIMOL, A., DIMOND, E. G. and SHEN, Y. Ejection time in aortic stenosis and mitral stenosis. *Am. J. Cardiol.*, 5: 728, 1960.
21. ALEXANDER, R. S. The genesis of the aortic standing wave. *Circulation Res.*, 1: 145, 1953.
22. BROCKENBROUGH, E. C., BRAUNWALD, E. and MORROW, A. A hemodynamic technic for detection of hypertrophic sub-aortic stenosis. *Circulation*, 23: 189, 1961.

Cardiac Involvement in a Peculiar Form of Paramyloidosis*

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PRIMARY AMYLOIDOSIS may be one of the causes of myocardial insufficiency.[1] A review[2] of seventy-one cases revealed that there was congestive cardiac insufficiency in 56 per cent. In the differential diagnosis of the etiology of congestive cardiac insufficiency of obscure origin the possibility of primary amyloidosis must not be overlooked. Clinically and electrocardiographically it also may simulate myocardial infarction or chronic constrictive pericarditis. Pericardiotomy has been carried out in a case of paramyloidosis because of a mistaken diagnosis of constrictive pericarditis.[3]

CLINICAL FEATURES

We may divide primary amyloidosis into two distinct types with different clinical and pathologic features. The first, corresponding to paramyloidosis, has evolved as a serious "heart disease" in which cardiac symptoms and clinical, hemodynamic and electrocardiographic signs depend on the amount and the distribution of amyloid substance in the myocardium. The electrocardiographic changes may resemble those of myocardial ischemia and infarction.[4] When the amyloid process is more generalized the clinical features may resemble those of constrictive pericarditis. The second type is a peculiar form of primary amyloidosis common in Portugal.[5–9] Publishing seventy-four cases in 1952, Andrade[10] made the diagnosis for the first time in Portugal.

The main features of this second type of amyloidosis are a familial relationship and involvement of the peripheral nervous system. The disease, beginning in the second, third or even fourth and fifth decade of life, is progressive.

The clinical picture includes gastrointestinal disturbances, alterations of sensibility and motility of polyneuritic type, sexual impotency in men, sphincter alterations, and trophic lesions of the skin and of the skeleton in the form of perforating ulcers of the foot or mutilation of the toes or of the metatarsus, as we noted in two cases. The gastrointestinal disturbance is fundamental. We observed a malabsorption syndrome, which was confirmed by xylose tolerance test (Benson's method). The neurologic alterations begin in the extremities of the legs. Sensitivity to heat and pain is first affected; then sensitivity to touch; and later deep sensitivities, especially postural sense. Motor disturbances usually begin in the extensor muscles of the feet and have the characteristics of peripheral paralysis with atrophy and disappearance of the tendon reflexes. None of our cases of this type showed macroglossia; in one there was atrophy of the tongue. In cases studied in our department the Congo red test (Benhold) proved to be of no value in diagnosis. Biopsy of the skin confirmed the diagnosis of amyloidosis in most of the cases.

CARDIAC MANIFESTATIONS

We have studied the cardiac manifestation of thirty-four cases. None of the thirty-four patients had symptoms of congestive cardiac insufficiency but three complained of precordial pain. None showed other clinical symptoms of myocardial involvement. Since the clinical picture was dominated by the neuropathy, some symptoms of myocardial insufficiency may have been masked by the neuromuscular alterations. The patients showed no alterations of cardiac sounds except two with a loud second aortic sound. The blood pressure reached 200/100 mm. Hg in one patient but was normal or low in all the others.

X-ray examination showed either a slight in-

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TABLE I
Cardiac Catheterization Findings in Three Cases

Case No.	Pressure (mm. Hg)	
	Right Ventricle	Right Atrium
7	36/10	10/4
16	37/10	10/2
20	36/12	10/4

crease in the size of the heart or distinct hypertrophy of the left ventricle. In one patient the ascending aorta was dilated and in two, the branches of the pulmonary artery were well marked.

Hemodynamic Changes: Right heart catheterization in three cases (Table I) disclosed signs of impaired diastolic filling, as seen in constrictive pericarditis. The right ventricular diastolic pressure was increased in all three cases; the systolic pressure was slightly above normal levels.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram and vectorcardiogram may disclose important alterations which escape clinical detection. These include disturbances of rhythm, changes in the P waves, P-R interval, voltage and duration of QRS, and S-T segment, deviation of the mean ventricular electrical axis, as well as the characteristic signs of localized damage to the myocardium.

Electrocardiograms were obtained on thirty-four patients with this special type of paramyloidosis. Sinus rhythm was present in all. Twenty of the thirty-four patients showed important alterations, including extrasystoles, left ventricular hypertrophy, right ventricular hypertrophy, incomplete A-V block, right bundle branch block, left bundle branch block and signs of ischemia (Table II). The electrocardiographic alterations represent the different localizations of the amyloid substance in

TABLE II
Electrocardiographic and Vectorcardiographic Alterations in Twenty Cases of Paramyloidosis

Case No.	Age (yr.) and Sex	Predominant Clinical Findings	Electrocardiogram	Vectorcardiogram	Biopsy
1	35, M	Peculiar peripheral neuropathy	P-R increased (0.24 sec.); LBBB, LVH	LBBB, LVH	Positive
2	34, M	Peculiar peripheral neuropathy	P-R increased (0.24 sec.); LBBB, LVH	LBBB, LVH	Positive
3	34, M	Peculiar peripheral neuropathy	Ventricular waves decreased in the peripheral leads	...	Positive
4	34, M	Peculiar peripheral neuropathy	LVH	...	Positive
5	64, F	Peculiar peripheral neuropathy	Disturbance of intraventricular conduction	...	...
6	33, M	Peculiar peripheral neuropathy	LBBB, LVH	LBBB, LVH	Positive
7	60, M	Peculiar peripheral neuropathy; mutilation of the toes and metatarsus	P-R increased (0.30 sec.); RBBB	RVH and disturbances of conduction of final portion of QRS loop	Positive (autopsy)
8	38, M	Peculiar peripheral neuropathy	RBBB	...	Positive
9	41, M	Peculiar peripheral neuropathy	LVH	LVH	Positive
10	65, M	Peculiar peripheral neuropathy	P-R increased (0.26 sec.); sinus block	...	Positive
11	43, M	Peculiar peripheral neuropathy	P-R increased (0.24 sec.)	...	Positive
12	28, M	Peculiar peripheral neuropathy	Primary alterations of repolarization	...	Positive
13	46, F	Peculiar peripheral neuropathy	Ventricular premature beats; P-R increased (0.24 sec.)	...	Positive
14	33, M	Peculiar peripheral neuropathy	Atrial premature beats; incomplete A-V block; LVH	LVH	Positive
15	46, M	Peculiar peripheral neuropathy	Atrial premature beats; LVH	...	Positive
16	29, M	Peculiar peripheral neuropathy	Incomplete A-V block; LVH	...	Positive
17	64, F	Peculiar peripheral neuropathy	Atrial premature beats; P-R increased (0.24 sec.); RBBB	...	...
18	57, F	Peculiar peripheral neuropathy; hypertension (blood pressure, 200/100 mm. Hg)	Atrial premature beats; sinus bradycardia; U wave greatly increased; LVH	Decrease of terminal conduction. LVH	Positive
19	54, F	Peculiar peripheral neuropathy	LVH	LVH	...
20	61, M	Peculiar peripheral neuropathy	LVH; sinus bradycardia	LVH	Positive

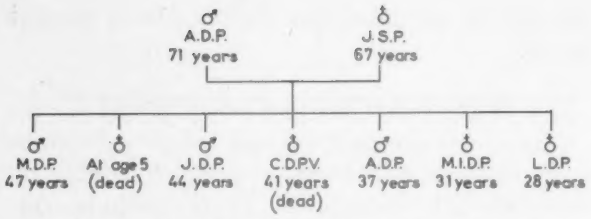


FIG. 1. Family tree of the patient in Case 1.

the myocardium, indicating predominant involvement of the specific tissues. *Vectorcardiograms* in eight of these twenty cases with electrocardiographic changes confirmed the diagnosis in some, altered it in others. Serial electrocardiograms demonstrated that the alterations in the myocardium were progressive. For example, a prolonged P-R interval later progressed to a more marked A-V block.

In this type of paramyloidosis the percentage of cases with cardiac involvement was very high but there was no close correlation between the degree of peripheral neuropathy and alterations of the myocardium. Cases with severe neuropathy may show very slight alterations in the electrocardiogram. Two patients died without showing clinical symptoms of congestive cardiac failure. At postmortem examination we studied the morphologic and histologic aspects of the heart and the distribution of amyloid substance in the heart.

ILLUSTRATIVE CASES

CASE 1. This was a 41 year old woman whose complaints of intestinal disturbances and paresis of the legs began 14 years previous to examination. Three years later she was insensible to a burn of the leg from an excessively hot heating pad. Painless ulcers on both legs and disturbances of the bladder developed. Her mother, two brothers (also examined by us) and two sisters had the same disease (Fig. 1).

Physical examination showed muscular atrophy of the small muscles of the hands, especially of the thenar eminences and first interosseous region; syringomyelitic dissociation of sensibility in the arms and thighs; paralysis of extensor movements of feet and toes; paralysis of flexion of feet and legs; trophic alterations of the toes and total anaesthesia of the legs. Edema of the face and legs was evident. The blood pressure was 160/100 mm. Hg. X-ray films of the chest showed slight cardiomegaly. The patient died 24 hours after entering the hospital, before any other examinations could be made.

Pathological Diagnosis: Autopsy revealed atrophy of the muscles, especially of the limbs; enlargement of the cardiac cavities; stasis of the liver; bilateral hydrothorax; hydropericardium; decubital ulcers in the gluteal region; foci of bronchopneumonia in the right inferior lobe.

Macroscopic Description of the Heart: The heart was slightly larger than the body's fist, weighing 345 gm. The cardiac cavities were slightly larger than normal. The wall of the left ventricle was 1.5 cm. thick at the base and 0.8 cm. at the apex, the wall of the right ventricle was 0.7 cm. in thickness. All valves and valvular orifices were within normal limits. The endocardium was greyish white and thickened, especially in the atria. The myocardium was pale red with no amyloid foci. Lugol's test was negative.

Microscopic Examination: Tricuspid and mitral valves. In both valves there were large quantities of amyloid substance in the form of large and small irregular blocks, especially on the surface. The deposits were especially heavy in the mitral valve. The fixed cells were greatly diminished in number. *A papillary muscle* showed very extensive deposits of amyloid substance; the muscular fibers had disappeared almost entirely, leaving only a few nuclei, not proliferated. There was no inflammatory reaction.

Left atrium. The endocardium (Fig. 2A) was considerably thickened and showed numerous accumulations of amyloid substance in blocks of varying shapes and forms spread diffusely through the whole thickness. The myocardium (Fig. 2B) showed deposits in a ring around the muscular fibers corresponding to sarcolemma. The greater quantities of the substance were in the subendocardial regions. The muscular fibers surrounded by the amyloid substance showed varying degrees of alterations: pyknosis, chromatolysis and karyolysis (Fig. 2C). Some were merely reduced to sarcoplasm or had even completely disappeared, leaving only the amyloid ring (Fig. 2D). There were no proliferations of the nuclei of sarcolemma nor of the fixed elements of the connective tissue; there was no inflammatory reaction.

Left and right ventricles. The findings were similar to those in the atrium in both myocardium and endocardium (Fig. 3A). The greater quantities of amyloid substance and the correspondingly graver alterations of the muscular fibers were in the subendocardial regions. Moderate quantity of amyloid substance was present in the vessels (Fig. 3B). The septum showed the same alterations, particularly in the muscular fibers in the subendocardial regions. Amyloid substance was noted in the vessels and nerves of the epicardium (Fig. 3C). In the epicardium there was mucoid infiltration.

Summary of Pathologic Findings: The heart showed a degree of hypertrophy with amyloid deposits in the tricuspid and mitral valves, in the endocardium (thickened) and in the myocardium especially in the subendocardial zone. There were alterations in the muscular fibers and moderate amyloid deposits in the vessels.

CASE 2. A 60 year old man (Case 2, Table 1) entered the hospital for the first time in 1956, complaining of diarrhea, urinary incontinence and diffi-

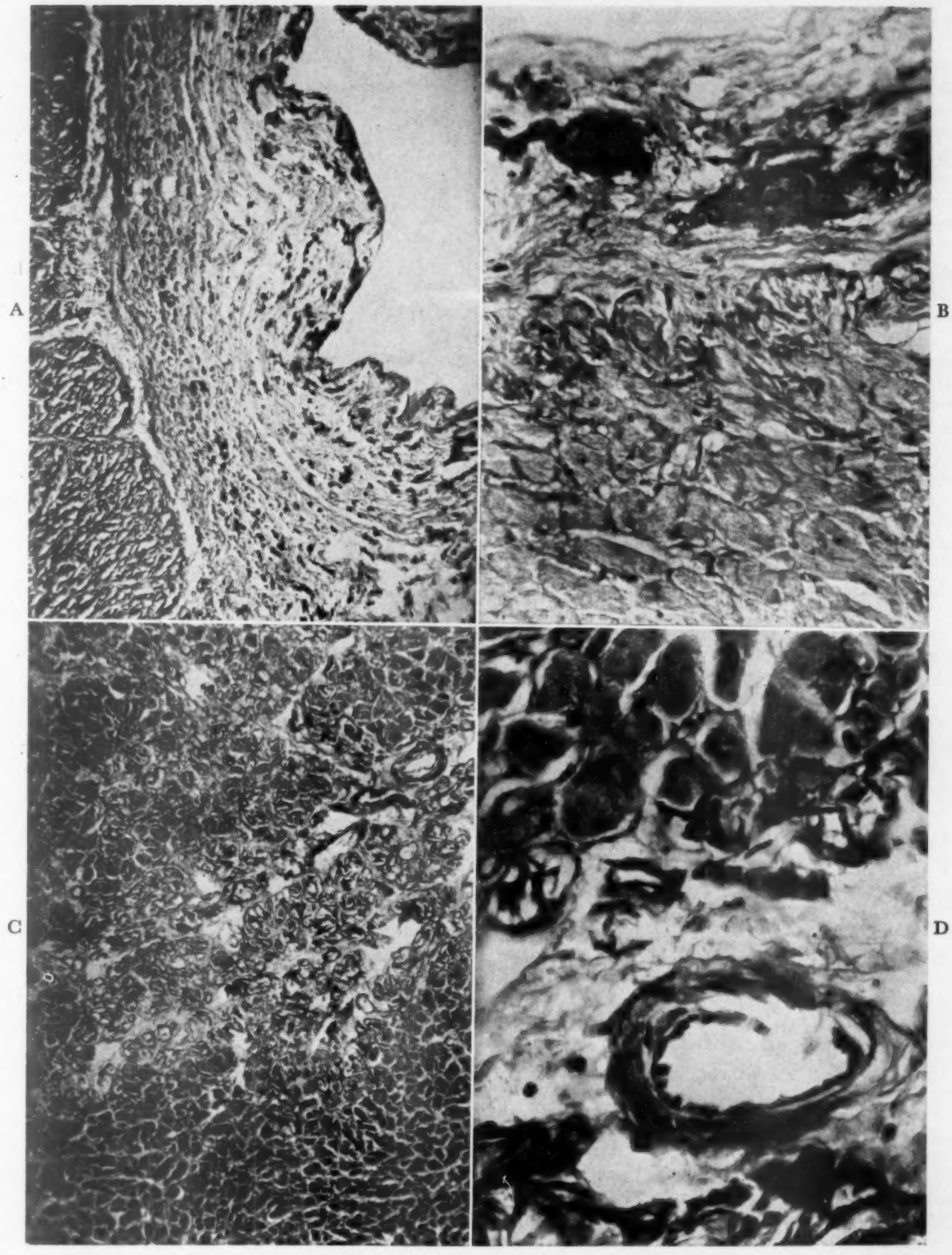


FIG. 2. A, thickened endocardium with extensive amyloid deposits. B, amyloid deposits in the endocardium and subendocardial portion of the myocardium. C, transverse cut showing amyloid deposits in ring form around muscular fibers. D, detail of (C). Amyloid deposits on wall of vessels.

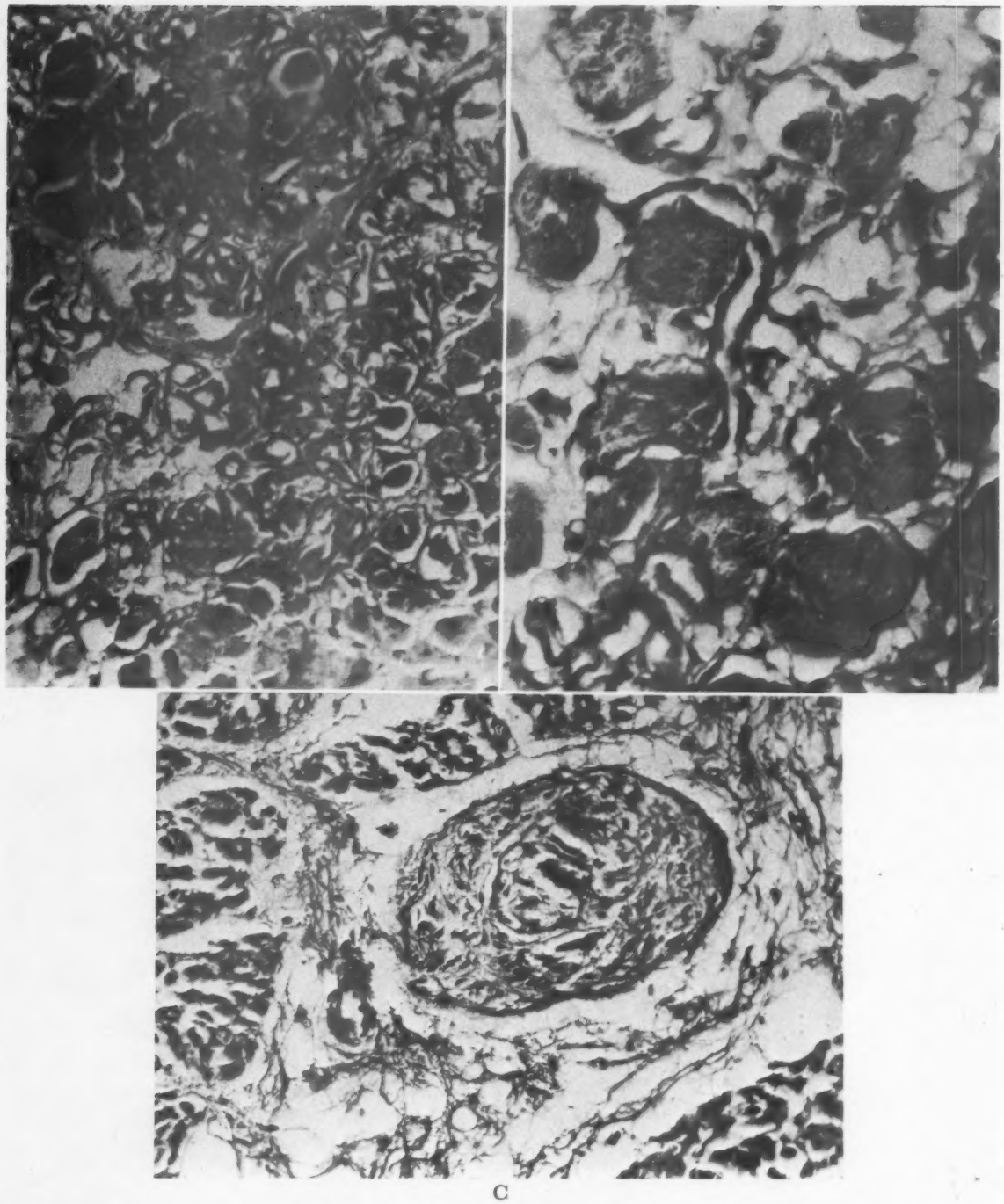


FIG. 3. Case 1. A, detail of amyloid deposits in ring form. Note that many of the muscular fibers are atrophied and in some cases have disappeared completely. B, another aspect of the ring form. C, amyloid deposit on the endoneurium of a nerve bundle of the myocardium.

culty in walking caused by bilateral partial mutilation of toes. He died suddenly in 1960. The presenting illness began 10 years previous to the hospital admission, with complaints of paresthesia and burning sensation in the legs and feet and intermittent claudication. One year later the patient noticed the appearance of an infected but indolent wound of the left big toe. Subsequently, similar wounds began to appear in all toes; the wounds suppurated abundantly and were accompanied by spontaneous painless elimination of osseous sequestrae. After 3 years the patient complained of nonbloody diarrhea which proved resistant to treatment. By that time he noticed visual disturbances and progressive sexual impotence with loss of libido and difficulty in erection.

Physical Examination: Clinical observation showed an emaciated patient, with pale skin and mucous membranes. He was without macroglossia. Cardiac and pulmonary examination were not remarkable. Blood pressure was 105/60 mm. Hg. The liver, spleen, kidneys and lymph glands were not enlarged. *Neurologic examination* disclosed decreased sensitivity to temperature and pain in the arms, with conservation of perception of touch. There was total anesthesia of the legs (involving sensations of temperature, pain and touch), suppression of deep sensibility and pressure perception and abolition of patellar reflexes. *Ophthalmologic examination* disclosed normal pupillary reflexes. There were white hyaline deposits at the level of the pigmented border of the pupillary margin (hyalinosis); scattered pigment in the anterior crystalloid layer; diffuse opacities of the crystalline lens; slightly deranged vitreous substance, without free opacities. The fundi were normal, showing only a decrease in pigmentation which clearly allowed the examination of the vessels of the uveal tract.

Laboratory Examinations: Blood count: red blood cells 2.7 million per cu. mm.; hemoglobin 53 per cent; color index 0.96; white blood cells 4,600 per cu.mm.; differential count: polymorphonuclear neutrophils 42 per cent, eosinophils 1 per cent, basophils 1 per cent, lymphocytes 47 per cent, monocytes 9 per cent. Erythrocyte sedimentation rate (Westergren): first hour, 108 mm.; second hour, 130 mm. Congo red test: 87 per cent dye retention after 60 minutes. Total serum bilirubin (30 minutes), 3.4 mg. per 100 ml. Cephalin-cholesterol flocculation test positive; thymol turbidity test, 6 units. Serum total cholesterol 148 mg. per 100 ml.; cholesterol esters 89 mg. per 100 ml. Serum amylase 80 Somoggi units per 100 ml.; serum lipase 0.2 units per 100 ml. Glucose tolerance curve: fasting, 74 mg. per 100 ml.; 30 minutes, 150 mg.; 60 minutes, 114 mg.; 120 minutes, 67 mg.; 180 minutes, 60 mg.

ACTH test (Thorn): before ACTH injection, eosinophils 137 per cu. mm.; 4 hours after ACTH injection, eosinophils 75 per cu. mm. Serum proteins, total 7.6 gm. per 100 ml.; albumin, 2.25 gm.; globulins 5.35 gm. Serum protein electrophoresis: albumin, 34 per cent; α-globulin, 5.3 per cent, α_2 globulin, 12.4 per cent; β-globulin, 14.4 per cent; γ-globulin, 33.6 per cent. Serum glycoprotein electrophoresis: albumin 2.3 per cent; α-globulin 29.6 per cent; α_2-globulin 29.6 per cent; β-globulin 24.2 per cent; γ-globulin 15.2 per cent. Serum lipoprotein electrophoresis: α-globulin 18.5 per cent; β-globulin 74.7 per cent; chylomicrons, 7.5 per cent.

Serum CO_2 "combining power," 19.6 mEq. per L.; potassium, 6.53 mEq. per L.; chloride 116.7 mEq. per L.; sodium 134.5 mEq. per L.; urea nitrogen 55 mg. per 100 ml. Urinalysis: specific gravity 1.010, reaction acid, proteins 0.1 gm.; creatinuria, 0.73 mg. per 24 hours; 17 ketosteroids, 1.9 mg. per 24 hours; hydroxycorticosteroids, 10.2 mg. per 24 hours; Bence-Jones proteinuria negative. Intestinal absorption: no data could be obtained in favor of malabsorption syndrome.

Radiologic Examinations: Radiogram of the thorax showed no alterations of the cardiac shadow or lung fields. Results of radiograms of the stomach and duodenum were within normal limits. Deficient impregnation of the intestinal wall by the contrast substance was observed. Radiograms of the skeleton showed periosteal ossification of the soft parts, especially at the level of the right hip joint; slight increase of the inferior medullary cavity of the antibrachial bones; medullary widening of the inferior femoral diaphysis; large osseous deformities of the metatarsophalangeal region and slight spondylarthrosis.

Electrocardiogram: The pattern of complete right bundle branch block was present. The vectorcardiogram showed evidence of right ventricular hypertrophy and impaired conduction in the final portion of the QRS loop.

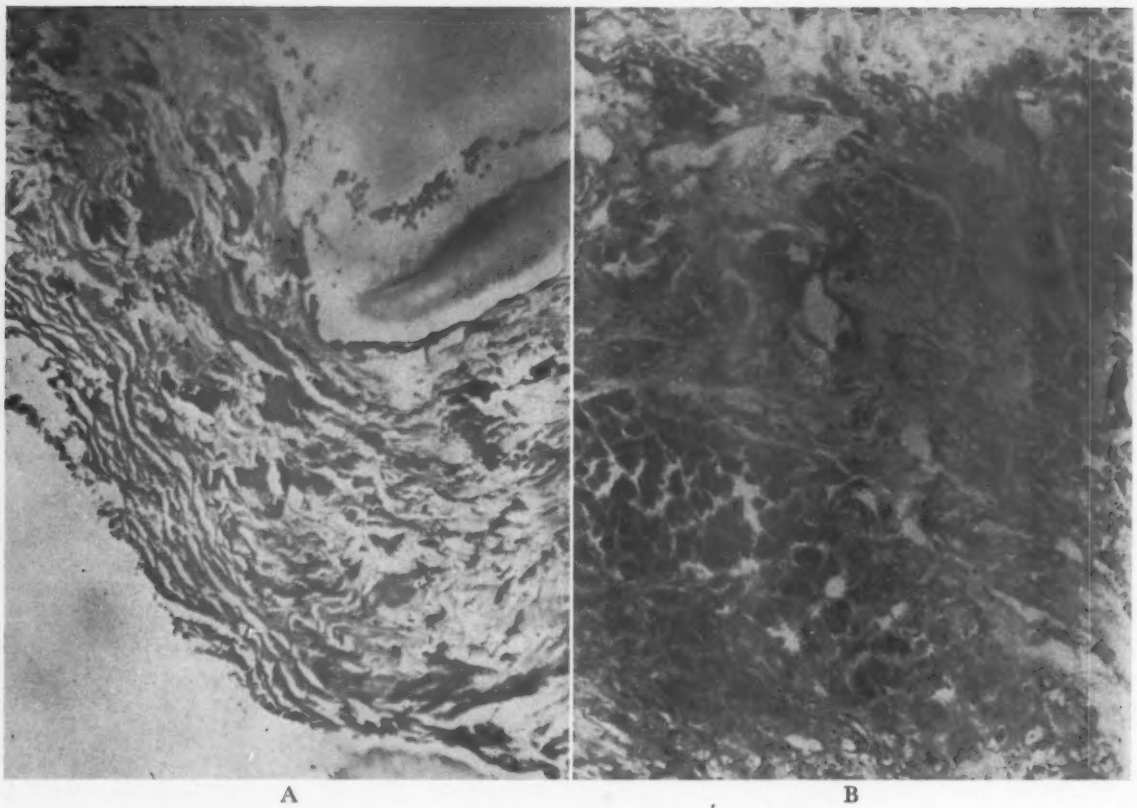
Tissue Biopsies: Muscle biopsy. Deposits of paramyloid substance were noted in the skin, aponeurosis and interstitial tissue of one muscle. Characteristic accumulations of paramyloid material were found in three nerves. Muscle atrophy was noted. *Testicular biopsy.* Deposits of amyloid substance were noted in the vessels. *Liver biopsy.* Nodular reticular proliferation (reticuloendothelial nodes) and foci of hyperplasia of the Kupffer cells were noted. Amyloid substance was present in the arterioles of the portal spaces.

Cardiac Catheterization: Pulmonary blood: oxygen saturation, 70 per cent; oxygen content, 9.2 volumes per 100 ml. Arterial blood: oxygen saturation, 95 per cent; oxygen content, 12.4 volumes per 100 ml.

"Pulmonary capillary" pressure, 11/7 (9) mm. Hg; pulmonary artery pressure, 18/9 (12) mm. Hg; right ventricular pressure, 36/10 mm. Hg; right atrial pressure, 10/4 (7) mm. Hg. Cardiac output (Au^{198}), α-0.993; hepatic blood flow (Au^{198}) K-0.1715.

Pathologic Diagnosis: Necropsy disclosed absence of the right fifth toe and left first toe; extensive trophic lesions of the skin in the feet; marked congestion of the intestinal mucosa; slight bilateral hydrothorax; bilateral cylindrical bronchiectasis; bilateral pulmonary emphysema; edema of the lower lobes of the lung and decubital ulcers.

Macroscopic Description of the Heart: The size of the heart was the same as the fist, weighing 275 gm. The cusps of the aortic, tricuspid and mitral valves showed slight thickening of their faces due to the presence of a pinkish-gray opaque tissue. The cardiac cavities were of normal size. The wall of the left ventricle was slightly thickened. The myocardium was soft in consistency and had a brownish-gray color. The coronary arteries were sinuous but had



A B

FIG. 4. Case 2. A, tricuspid valve. Extensive amyloid deposits in the myocardium. B, left ventricle. Amyloid deposits in the myocardium in the form of small rings.

no atheromatous plaques. The initial portion of the aortic arch showed no alterations, except a reddish color of the intimal layer.

Microscopic Examination: Right atrium. There were extensive accumulations of amyloid substance in the greatly thickened intimal layer. These deposits formed a continuous layer in certain places (Fig. 4A). The epicardium was narrow and also showed amyloid accumulations. In the myocardium, the amyloid substance was present in significant amounts and was arranged between the muscle fibers, forming a border around them. The muscle fibers so encircled showed alterations ranging from simple atrophy to complete disappearance. In the latter case, the amyloid substance either completely replaced the muscle fiber or more frequently, was disposed around an empty space ("ring images"). Between these two extreme stages some intermediary aspects were observed, consisting of sarcoplasm with pyknotic nuclei or even without nucleus.

Right ventricle. There were important accumulations of amyloid substance in the endocardium and myocardium, disposed mainly around the muscle fibers which lay nearest to the endocardium. There were vascular deposits which, however, did not obstruct the vascular lumen. The alterations of the muscle fibers in the places where the amyloid substance accumulated were similar to those described for the atrium. In the ventricle, however, there was a more or less extensive atrophy of these fibers, even where extravascular accumulation of the amyloid material was not present.

Left atrium. Findings in the left atrium were similar to those in the right ventricle. There were similar extensive deposits of the amyloid substance in the thickened endocardium and between the myocardial muscle fibers, particularly the longest ones. The lesions of the muscle fibers were similar to those described for the right ventricle.

Left ventricle. Extensive foci were present constituted by an amorphous, homogenous and eosinophilic substance and stained red by Congo red and gentian violet dyes. In these places, the muscle fibers were atrophied and in many sites were completely absent (Fig. 4B). In transverse cuts of the myocardial muscular fibers, there were deposits of the substance described previously which assumed the form of a ring. These rings were empty or encircled a muscle fiber in a more or less advanced state of atrophy. In the subendocardial portion of the myocardium, this substance often constituted a continuous accumulation assuming the aspect of a band with very definite limits. Focal or diffuse accumulations of the same material were observed in the wall of some myocardial arteries and veins. Similar deposits were also found in the endocardium. In the pericardium some small accumulations of the same material were also found in the wall of some vessels.

Septum. The accumulations of amyloid substance were also very extensive in the interventricular septum, particularly in the endocardium in which they were arranged as a continuous band following the contour of the cardiac cavity and bordering a certain distance from it. The amounts of amyloid material and the corresponding alterations of the muscle fibers were much more significant in the subendocardial layers.

Tricuspid and mitral valves. In both atrioventricular valves the amyloid deposits were very prominent, and the amyloid substance was arranged either in isolated masses of various sizes or acquired a restricted aspect at the surface; the cells (fibrocytes and fibroblasts) were very scanty (Fig. 4A).

Summary: There were extensive accumulations of amyloid substance in all layers of the heart, especially the endocardium and the subendocardial muscle fibers. Vascular deposits were present, especially in the greater vessels, but they were not very important and never caused obstruction of the vascular lumen. However, several zones in the right ventricle showed very significant atrophy of the muscle fibers in which accumulations of the amyloid material was not present. Inflammatory reactions or foreign body reactions due to the presence of the amyloid material have not been observed.

Comments

The incidence and the degree of cardiac involvement are closely related to the anatomicoclinical type of amyloidosis. The larger deposits of the amyloid substance occur in the first type of paramyloidosis[11–20] and frequently the alterations in the heart may predominate over involvement of other organs.[21–29] The heart is also a constant site of amyloid deposits in the second type of paramyloidosis, however. In the first postmortem study of this condition made in Portugal, Wohlwill[30] referred to the presence of deposits in the pericardium and myocardium. Furtado, Gonçlaves and Carvalho[6] confirmed this and Horta[8] again called attention to the importance of cardiac involvement. The macroscopic appearance of the heart is similar to that in the first type of paramyloidosis. The heart is usually somewhat larger than normal, the cavities are dilated and the ventricular walls are thickened. The myocardium, especially in the ventricles, may be rather rigid but generally not to the extent that the cavities of the heart fail to collapse when the heart is taken from the body, as happens in the severe cardiac forms of the first type. Sometimes the myocardium is greyish-red and may have yellow patches. In no case did we observe a clearly lardaceous aspect; Lugol's test also was regularly negative. The atrial endocardium showed over-all thickening; one case had small transparent pink nodules and wheals in the pericardium.

Microscopic examination showed that the substance is deposited in the layers of the heart as in the first type of paramyloidosis. In the endocardium, which is generally thickened and edematous, we found deposits in the form of lumps or bands of varying sizes and shapes, and sometimes arranged in layers. In the pericardium the substance was generally in the walls of the vessels and in the fascicule of the nerves. These deposits in the nerves may be found in the perinervium or in the endonervium, and in the latter case, either inside or outside the vessels, in the form of spheres. In the myocardium the deposits occur either in the interstitium or in the walls of the vessels. The only difference from the serious cardiac forms of the first type is that the deposits are smaller. We must, however, call attention to the frequency with which deposits were observed in the subendocardial portion of the myocardium and to the fact that in all the cases these deposits occurred in a continuous band of fairly regular thickness.

Summary

Heart disease is common in paramyloidosis. The clinical and pathologic features can be divided into two fundamental types. In the first type serious cardiac insufficiency is predominant and the patients die from congestive heart failure. The second type is familial, a peculiar peripheral neuropathy is the predominant lesion and patients die from cachexia. Patients with the first form may present a clinical, electrocardiographic and hemodynamic picture simulating ischemia or infarction of the myocardium or chronic constrictive pericarditis, or diffuse fibrosis of the myocardium. Patients of the second type have cardiac abnormalities in the electrocardiogram such as right or left bundle branch block, left ventricular hypertrophy, atrioventricular dissociation and signs of ischemia. The Congo red test is usually negative.

It is almost always possible to diagnose cardiac paramyloidosis of the first or second form in living patients by biopsy of the skin.

References

1. Thomashow, A. I., Angle, W. D. and Morrione, T. G. Primary amyloidosis. *Am. Heart J.*, 46: 895, 1953.
2. Higgins, W. H. and Higgins, W. H., Jr. Primary

amyloidosis. A clinical and pathological study. *Am. J. M. Sc.*, 220: 610, 1950.
3. Benson, R. and Smith, J. F. Cardiac amyloidosis. *Brit. Heart J.*, 18: 529, 1956.
4. Coelho, E. and Pimentel, C. Alterations physiopathologiques et anatomiques de la fibrose et de l'amyloidose diffuse du myocarde. Semaine hôp. Paris, 35: 709, 1959.
5. Andrade, C. de. Note préliminaire sur une forme particulière de neuropathie. *Rev. neurol.*, 85: 302, 1952.
6. Furtado, D., Gonçalves, A. and Carvalho, O. Paramiloidose de forma nevritica. *J. Medico*, 515: 977, 1952.
7. Horta, J. S. Pathologische Anatomie der Portugiesischen Paramyloidosen. Fälle mit Besonderer Bevorzugung des Peripheren Nervensystems. *Gaz. med. port.*, 9: 678, 1956.
8. Horta, J. S. and Dias-Coelho, M. R. Localisation de substance paramyloide dans le système nerveaux central. *Arch. de Vecchi anat. pat.*, 31: 163, 1960.
9. Rosário, M. A. R., Antunes, J. L. and Barros, F. Contribuição para o estudo clinico e laboratorial da paramiloidose de Corino de Andrade. *J. Soc. Ciencias Med.*, 125: 1, 1961.
10. Andrade, C. de. A peculiar form of peripheral neuropathy: familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain*, 75: 408, 1952.
11. Wild, C. Beitrag zur Kenntnis der Amyloiden und der Hyalinen Degeneration des Bindegewebes. *Beitr. path. Anal.*, 1: 175, 1886.
12. Steinhaus, F. Am Circulations und digestions Apparat. *Ztschr. klin. Med.*, 45: 375, 1902.
13. Silver, H. and Lindblom, A. F. Ein Fall allgemeiner Amyloidose ohne nacheisbare Ursache (sogenanten "idiopatische" Amyloidose). *Acta med. Scandinav.*, 64: 529, 1926.
14. Lubarsh, O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen. *Arch. path. Anat.*, 271: 867, 1929.
15. Reimann, H., Kouchy, R. and Eklund, C. Primary amyloidosis limited to tissue of mesoderma origin. *Am. J. Path.*, 11: 977, 1955.
16. Dillon, J. H. and Evans, L. R. Primary amyloidos s: a report of three cases. *Ann. Int. Med.*, 17: 722, 1942.
17. Lindsay, S. and Knosp, W. T. Primary systemic amyloidosis. *Arch. Path.*, 39: 315, 1945.
18. Findley, J. and Adams, W. Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia. *Arch. Int. Med.*, 81: 342, 1948.
19. Iverson, L. and Morrison, A. Primary systemic amyloidosis. *Arch. Path.*, 45: 1, 1928.
20. Williams, A. W. Primary amyloidosis with renal and myocardial failure. *J. Clin. Path.*, 5: 54, 1952.
21. Kann, G. Ein Fall von isoleiter Amyloidose des Herzens. *Virchow's Arch. path. Anat.*, 237: 22, 1922.
22. Larsen, R. A pathological study of primary myocardial amyloidosis. *Am. J. Path.*, 6: 147, 1930.
23. King, L. S. Atypical amyloid disease with observations on a new stain for amyloid. *Am. J. Path.*, 24: 1095, 1948.
24. Ballinger, J. Amyloid heart disease. *Am. J. M. Sc.*, 217: 308, 1949.
25. Hulbert, B. and Meyer, H. M. Primary amyloidosis of heart. *Am. Heart J.*, 38: 604, 1949.
26. Jones, R. and Frazier, D. Primary cardiovascular amyloidosis. *Arch. Path.*, 50: 366, 1950.
27. Josselson, A., Pruitt, R. and Edwards, J. Amyloid localized to the heart. *Arch. Path.*, 54: 359, 1952.
28. Smith, J. M. Primary (atypical) localized amyloidosis of heart. Case report. *U. S. Armed Forces M. J.*, 2: 723, 1951.
29. Mulligan, R. Amyloidosis of the heart. *Arch. Path.*, 65: 615, 1958.
30. Wohlwill, F. Formas atipicas da amiloidose. *Amatus Lusitanus*, 1: 373, 1942.

Ventricular Aneurysm

Fourteen Cases Subjected to Cardiac Bypass Repair Using the Pump Oxygenator*

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SERIOUS AND even fatal cardiac lesions may result from myocardial necrosis in patients surviving the initial episode of coronary occlusion. Among the lethal complications are rupture of the ventricle, perforation of the ventricular septum, rupture of a papillary muscle, mural thrombosis with embolization, and ventricular aneurysm. The most common of these complications is aneurysm of the left ventricle which has been reported in 10 to 38 per cent of patients.[1–4] The diagnosis frequently may be made early by the characteristic electrocardiographic and roentgenographic findings. However, many cases go undiagnosed and the patient later dies from congestive heart failure, rhythm disturbances, thromboembolic episodes and repetitive infarctions. Early recognition is becoming more important with the advent of successful cardiac surgery.

Sternberg[5] reported only three cases of ventricular aneurysm diagnosed antemortem until 1914. Early reference to cardiac aneurysm was made by Baillow,[6] Barrich,[7] Dionis,[8] and others during the seventeenth century, but these authors probably described other varieties of cardiac dilatation not secondary to myocardial infarction. Reports by Galeati[9] and John Hunter[10] in 1757 referred to the specific type of ventricular aneurysm which is a complication of myocardial infarction. John Hunter[10] described a lesion: "At the apex it was forming itself into a kind of an aneurysm becoming very thin; this part was lined with a thrombus just the shape of the pouch in which it lay." Cruveilhier[11] in 1816 first attributed the development of aneurysm to myocardial fibrosis more than 60 years before Cohnheim[12] introduced the modern concept of coronary sclerosis or thrombosis as a cause of myocardial ischemia. Sternberg[5] in the early twentieth century recognized four stages of its development: a stage of anginal attacks; a stage of infarction and pericarditis; a latent period; and a terminal phase of aneurysm development and congestive heart failure or sudden death. Moreover, he pointed out the pathologic correlation and potential value of roentgenography in its diagnosis. In 1922 Sézary and Alibert[13] were the first to diagnose a ventricular aneurysm by this means. Since that time the diagnosis has been simplified and other reports have appeared dealing with sizable series of cases which were diagnosed clinically.[14]

The origin of aneurysms of the ventricle may be congenital or acquired. In the latter instance the lesion may be secondary to trauma or coronary occlusion, but occasionally is due to gummatous syphilis, infective endocarditis or rheumatic necrosis of the myocardium. Sternberg[5] found that of 207 published cases of cardiac aneurysm, 174 (84.1 per cent) were due to coronary occlusion. Formation of a ventricular aneurysm following infarction is related to the distance the necrotic zone penetrates the myocardium. Inadequate rest and the presence of systemic arterial hypertension are important factors in the pathogenesis of ventricular aneurysm. Schlichter, Hellerstein and Katz[3] analyzed 102 cases of ventricular aneurysm and concluded that only twenty-four had adequate rest after the acute occlusion. In their series 67.7 per cent of the patients had diastolic hypertension and 26 per cent had valvular lesions which contributed to the cardiac work load. Aneurysms of the ventricle may develop within 2 days or as late as 10 years after the acute infarction.[15]

Pathologic findings in ventricular aneurysms vary widely. The right ventricle is rarely involved, Appelbaum and Nicolson[1] reporting only one out of fifty-six cases in their series. In

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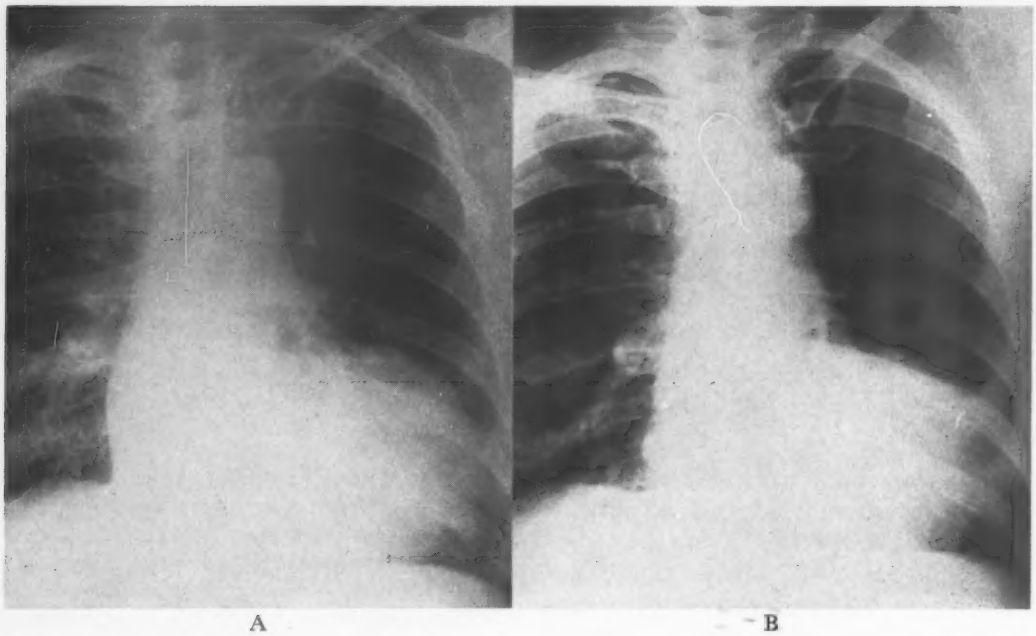


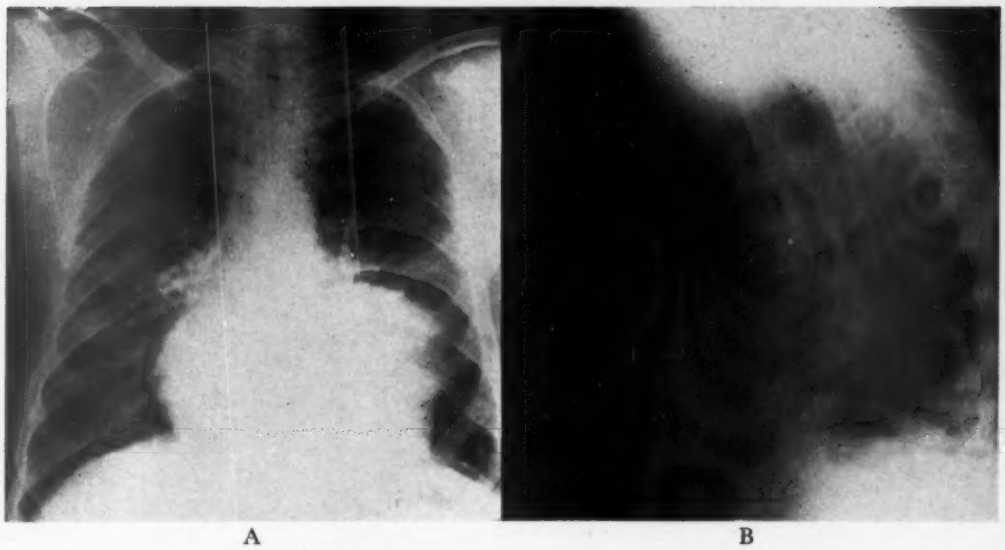
A B

FIG. 1. Case 1. Roentgenograms before and after excision of an aneurysm of the left ventricle. A, the aneurysm extends laterally and superiorly; paradoxical pulsation was evident fluoroscopically. B, 14 months after operation the cardiac silhouette has improved and moderate left ventricular hypertrophy persisted.

order of frequency the site of involvement in the left ventricle is the apex, anterior wall, posterior wall and finally the interventricular septum. Mural thrombosis is common; Schlichter[3] reported an incidence of 53.9 per cent in contrast to an incidence of 21.2 per cent in cases of myocardial infarction without aneurysm. Peripheral embolization from spontaneous dislodgment of thrombi is not uncommon, particularly in the presence of cardiac arrhythmia. Occasionally the clot becomes calcified and even ossified. Hanbury[16] reported the case of a patient with left ventricular aneurysm with calcification who survived 28 years after the original myocardial infarction. This lends support to the idea that calcification of the aneurysm indicates a favorable prognosis.

The prognosis varies widely depending upon the extent of the lesion, the degree of coronary insufficiency and the condition of the remainder of the myocardium. Master et al.,[17] in an extensive review of 553 patients with coronary occlusion or insufficiency, described ten patients with ventricular aneurysm. Four patients died; one patient, a physician, was alive and well 29 years after the acute occlusion. These authors stated, "The benign course of ventricular aneurysm in many patients is well known, and is borne out in our patients many of whom lived more than 10 years and have been working." Others have a less optimistic view of the prognosis in ventricular aneurysm. Schlichter et al.[3] stated that the prognosis was half as favorable in patients with an aneurysm following myocardial infarction as in others. In a collected series of cases with cardiac aneurysm, 73 per cent died within 3 years and 88 per cent died within 5 years. Of interest was the fact that rupture was a relatively infrequent cause of death in ventricular aneurysm. Appelbaum and associates[1] described only nine perforations in 150 cases. The cause of death in 70 per cent of Schlichter's[3] cases was congestive heart failure. Presence of the noncontractile sac in the anterior surface of the ventricle impairs the normal ejectile force of the left ventricle, significantly reducing cardiac output. For example, De Camp,[18] who employed cardiac catheterization in study of a patient with left ventricular aneurysm, demonstrated a cardiac output of 1.6 L. per minute compared to an expected normal output of 4 L. per minute.

Surgical treatment of aneurysm of the left ventricle was first attempted by Beck[19] in 1944. In this case he incised the pericardium around the aneurysm leaving the pericardium adherent to the lesion. A fascia lata graft was then sutured to the adherent pericardium and plication sutures were taken centrally to reduce the



A B

FIG. 2. Case 2. Roentgenograms of chest before excision of an aneurysm of the left ventricle. A, posterioanterior view. The aneurysm extends laterally and superiorly. B, lateral view. The aneurysm extends anteriorly.

size of the aneurysm and graft. The patient died 5 weeks later with empyema and encephalomalacia. Murray[20] 3 years later reported experimental excision of myocardial infarcts and demonstrated an increase in cardiac output by removal of the "expansion chamber." Bailey and associates[21] in 1958 reported surgical excision with ventriculoplasty in six patients with aneurysms secondary to myocardial infarction with five survivors. The first patient in their series was operated upon in 1954 with a good result. Likoff and Bailey[22] stated that the method of tangential excision with a special clamp was simple and effective and that the "flush out" technic controlled the problem of embolization from the mural thrombi. In their opinion the use of an open technic using cardiopulmonary bypass was not justified under these circumstances. In 1956 De Camp[18] operated upon a 65 year old patient by a similar closed technic, but the patient died 8 days after operation from hemorrhage and possible recent infarction.

We previously reported a successful excision of a massive left ventricular aneurysm using the pump oxygenator for temporary cardiopulmonary bypass in six patients with good recovery.[23] Open repair of left ventricular aneurysm was recommended because it permitted accurate excision of the sac, preserving functioning myocardium, papillary muscles and chordae tendineae of the mitral valve. Lillehei,[24] too, has used this method successfully.

CASE REPORTS

Fourteen patients undergoing excision of aneurysms of the left ventricle using the temporary cardiopulmonary bypass will be presented in detail, including the clinical and physiologic data, with a discussion of the possible effectiveness of surgical treatment and its influence upon cardiac function and survival.

CASE 1. I. N., a 50 year old man, was admitted to Methodist Hospital on January 13, 1958, with severe exertional dyspnea and a history of coronary occlusion 3 months previous to admission. Blood pressure prior to the infarction was 170/100 mm. Hg and at one time several years previously was recorded at 250 mm. systolic. After the infarction his blood pressure was stable at about 120/90. He remained in bed 10 weeks with congestive heart failure and angina pectoris relieved by digitalis and nitroglycerine.

Physical examination revealed moderate obesity and cardiac enlargement. The electrocardiogram disclosed an extensive infarction of the anterior wall and roentgenograms showed a large aneurysm of the left ventricle (Fig. 1A). Cardiac catheterization was not performed.

Operation was performed January 17, 1958, using complete cardiopulmonary bypass. The aneurysm was located in the anterior and apical portion of the left ventricle and was completely excised. Ventriculorrhaphy was performed on the large defect and recovery was satisfactory. He was dismissed from the hospital 18 days later.

Follow-up Study: A letter from his referring physician received March 16, 1959 stated that the patient was supporting himself as a truck farmer. He had

TABLE 1
Right Heart Catheterization Findings in Twelve Cases of Ventricular Aneurysm

Case No.	When Performed		Pressures (mm. Hg)			Cardiac Index (L./minute/M²)
			Pulmonary Capillary	Pulmonary Artery	Right Ventricle	
2	Before		30	66/32	68/4	1.59
	After (6 weeks)	R	10	25/10	25/0	1.84
		E	10	28/10	28/0	3.6
3	Before	R	18	40/20	40/5	1.5
		E				1.6
	After (2 months)	R	10	25/10	28/0	2.2
		E	13	38/14	38/0	3.7
4	Before	R	22	45/15	45/10	1.2
		E	30	60/18	60/10	1.4
5	Before	R	13	24/10	23/0	1.6
		E	Brachial artery	36/30	...	...
			Shock and ventricular tachycardia			
	After (2 months)	R	12	24/10	24/0	1.5
		E	13	25/10	26/0	1.8
6	Before	R	14	28/12	30/0	1.36
		E	28	60/20	60/5	2.72
7	Before		29	64/30 (E)		
				68/29	68/14	1.57 (R)
9	Before		25	47/18	46/0	1.2 (R)
				48/18	...	2.8 (E)
10	Before		21	40/21	41/18	Not done
11	Before		22	54/20	60/27	1.6 (R)
12	Before		40	65/25	65/10	1.4 (R)
13	Before			60/30	63/-	1.9 (R)
				70/40 (E)	...	2.5 (E)
14	Before		23	80/31	78/4	1.3 (R)

NOTE: R = resting; E = exercise.

mild complaints of dyspnea on exertion and pain in the chest. His blood pressure was 150/100 mm. Hg, and pulse rate 86. A roentgenogram of the chest showed a relatively normal cardiac silhouette (Fig. 1B).

CASE 2. W. M., a 48 year old man, was admitted to Veterans Administration Hospital on March 12, 1958, with the complaint of severe anginal pain in the chest requiring as much as twelve to fifteen nitroglycerine tablets daily for relief. The initial coronary occlusion occurred in 1948 although anginal pains had been present 3 years earlier. The patient experienced repeated bouts of anginal pain and coronary occlusion requiring bed rest and hospitalization on increasingly frequent occasions. He was dyspneic on mild exertion.

Physical examination revealed a blood pressure of 100/76 mm. Hg and evidence of left ventricular enlargement. The electrocardiogram demonstrated atrioventricular dissociation and extensive anteroseptal infarction. Roentgenograms of the chest (Fig. 2) showed a left ventricular aneurysm which on fluoroscopy appeared to have paradoxical pulsation.

Cardiac catheterization, performed March 24, 1958, revealed moderate pulmonary hypertension (66/32 mm. Hg) with reduced cardiac output and cardiac index at rest (0.59 L. per minute per M²) (Table 1).

Operation was performed on March 27, 1958, using the pump oxygenator for temporary cardiopulmonary bypass. A massive aneurysm of the left ventricle was excised, removing a sizable intraluminal thrombus (Fig. 3). The ventriculoplasty was extensive, being approximately 12 cm. long (Fig. 4). Recovery from operation was uneventful and he was discharged from the hospital June 6, 1958.

Follow-up Study: The patient has had dramatic relief of the incapacitating angina pectoris. Roentgenograms of the chest made 9 months later revealed reduction in the size of the heart with a more normal contour (Fig. 5). Cardiac catheterization 6 weeks after operation revealed a reduction in pulmonary arterial pressure to a normal level (25/10) and substantial increase in cardiac index (3.6 L.) (Table 1).

CASE 3. I. G., a 57 year old man, was admitted to Methodist Hospital June 26, 1958, with a history of an attack of acute myocardial infarction on January

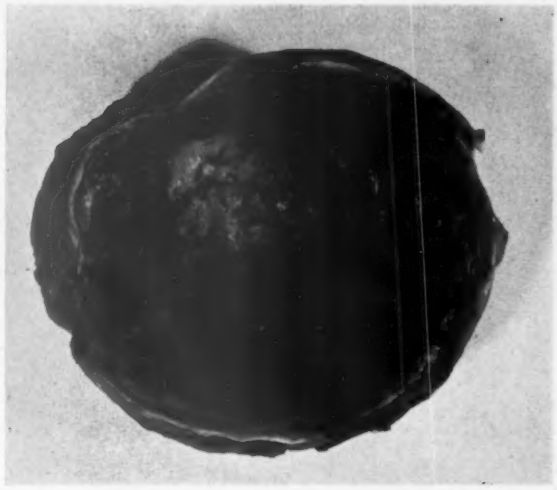


FIG. 3. Case 2. Specimen of aneurysm of left ventricle removed intact. The sac is composed predominantly of fibrous tissue and is partly lined by organizing and laminated thrombus.

FIG. 4. Case 2. Photograph of heart made at operation showing ventriculorrhaphy on anterior surface of left ventricle with multiple silk sutures.

15, 1958. He was hospitalized for 7 weeks, but thereafter he experienced dyspnea of increasing severity and moderate anginal pains in spite of medical therapy.

On examination, a blood pressure of 100/60 mm. Hg was recorded and there was evidence of cardiac enlargement. *Cardiac catheterization* (Table I) revealed mild pulmonary hypertension (40/20 mm. Hg) and moderately reduced cardiac output (cardiac index 1.5 L.)

Operation:. On July 1, 1958, excision of a massive aneurysm of the anterior and lateral surface of the left ventricle was performed during cardiopulmonary bypass. The lesion measured more than 10 cm. in diameter. Recovery following operation was satisfactory and the patient was dismissed from the hospital 12 days later.

Follow-up Study: Two months later he returned for cardiac catheterization which revealed a reduction of pulmonary arterial pressure to 25/10 mm. Hg. During exercise, the cardiac index increased 40 per cent (Table I). Nine months following operation the patient has only mild exertional dyspnea and no

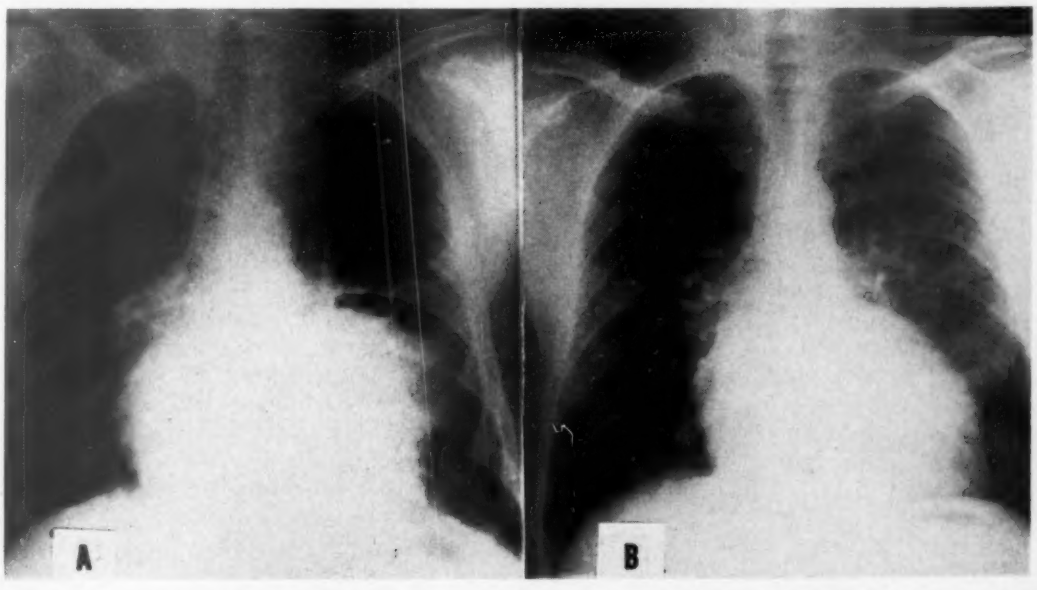
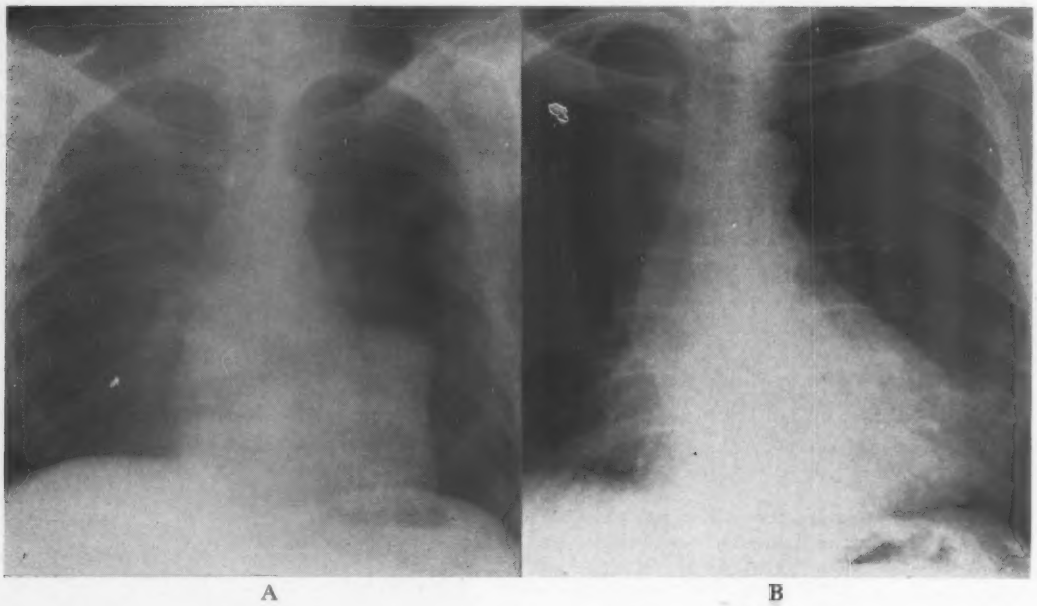


FIG. 5. Case 2. Roentgenogram of chest made before operation (A) and 5 months after operation (B) showing improved cardiac contour and reduction in cardiac size.



A B

FIG. 6. Case 4. Roentgenogram of chest before (A) and 8 months after operation (B). Removal of left ventricular aneurysm produced a marked improvement in cardiac configuration.

angina. Recent roentgenograms of the chest reveal only mild cardiac enlargement.

CASE 4. T. B., a 56 year old man, was admitted to Methodist Hospital with a history of myocardial aneurysm diagnosed 14 months previously. Following the original acute episode he was hospitalized for 29 days. Roentgenograms 9 months later revealed a ventricular aneurysm. Except for occasional cardiac arrhythmia his symptoms consisted only of mild dyspnea and chronic fatigue.

On admission to the hospital the blood pressure was 120/60 mm. Hg and there were no cardiac murmurs. No râles were audible in the lungs. Roentgenograms (Fig. 6) revealed an aneurysm on the lateral aspect of the left ventricle which appeared to pulsate paradoxically during fluoroscopy.

Cardiac catheterization revealed pulmonary arterial hypertension (45/15) which increased following exercise (66/18) and reduced cardiac index (1.2 L.) which did not increase during exercise (Table 1).

Operation: On August 1, 1958 a resection of a ventricular aneurysm measuring about 8 cm. in diameter was performed using the pump oxygenator for temporary cardiopulmonary bypass. Upon opening the aneurysm several loose thrombi of significant size were floating freely. These apparently were dislodged during dissection of the pericardium off the lesion. These and the attached thrombi were removed. The aneurysm was accurately excised and ventriculorrhaphy was performed. The patient made an uneventful recovery and was dismissed from the hospital 14 days later.

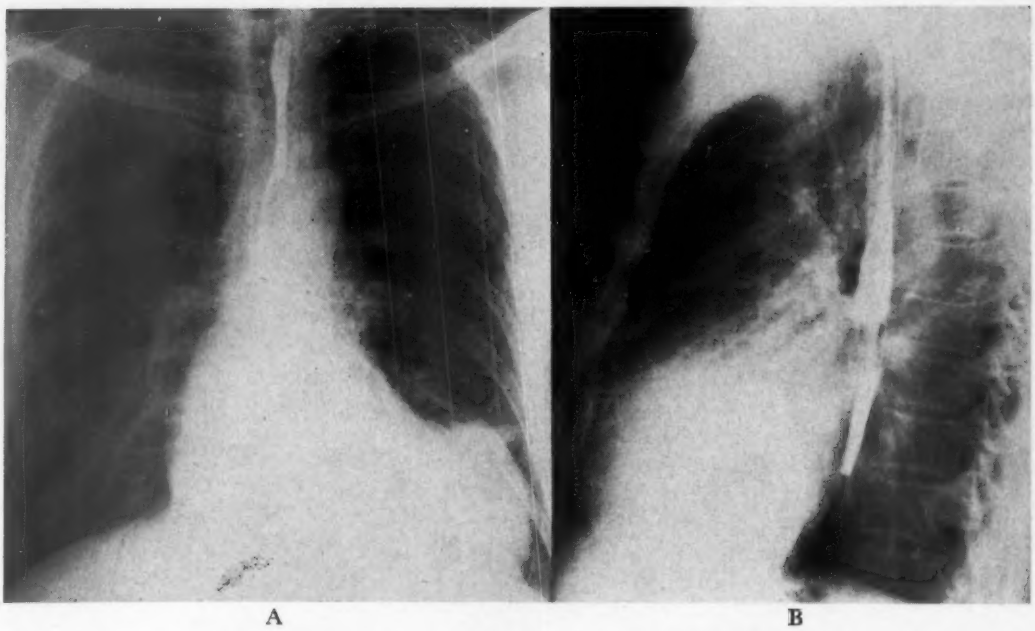
Follow-up examination 8 months later revealed continued clinical improvement. Roentgenograms of the chest showed an improved cardiac silhouette without aneurysm (Fig. 6). It is planned to repeat the cardiac catheterization if the patient consents.

CASE 5. L. U., a 45 year old man, was admitted to Methodist Hospital on October 12, 1958 with a diagnosis of aneurysm of the left ventricle. Until January 1, 1958, his health was excellent, but on this occasion he experienced the sudden onset of pain in the chest, diplopia and dizziness. Chest films made at that time were within normal limits. Following an automobile accident in June 1958, roentgenograms revealed a ventricular aneurysm. This lesion steadily increased in size until his admission to the hospital. His symptoms were of mild exertional dyspnea and minimal angina pectoris.

On examination, the blood pressure was 120/90 mm. Hg and moderate cardiomegaly without murmurs was noted. The electrocardiogram revealed elevated S-T segments in all precordial leads. *Cardiac catheterization* revealed a low cardiac index (1.6 L.) which was definitely reduced following exercise with normal resting pressures.

Operation: On October 13, 1958, excision of a large left ventricular aneurysm was performed utilizing the pump oxygenator for temporary cardiopulmonary bypass. The aneurysm itself was almost spherical measuring 10 cm. in diameter with significant paradoxical motion. The patient's course after operation was relatively uncomplicated and he was dismissed from the hospital on the twelfth day.

Follow-up Study: Two months later cardiac catheterization revealed good cardiac function with normal pulmonary arterial pressures before and after exercise. The cardiac index remained low (1.5 L.). After 5 months he had gained 10 pounds and felt much improved. His blood pressure was 150/90



A B

FIG. 7. Case 6. Roentgenogram of chest showing massive left ventricular aneurysm. A, postero-anterior view. B, lateral view.

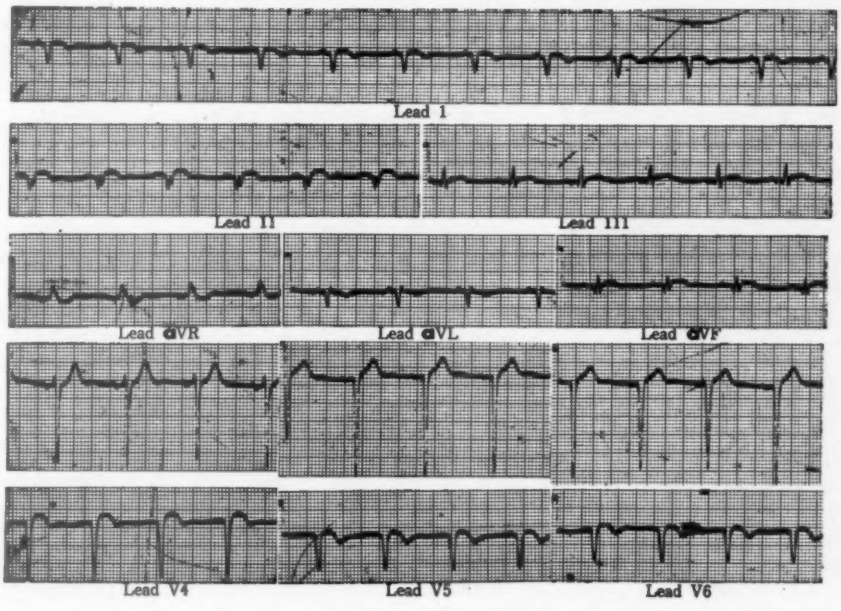


FIG. 8. Case 6. Electrocardiographic evidence of extensive anterior infarction with diaphragmatic involvement of indeterminate age. S-T segment elevation was consistent with a diagnosis of ventricular aneurysm.

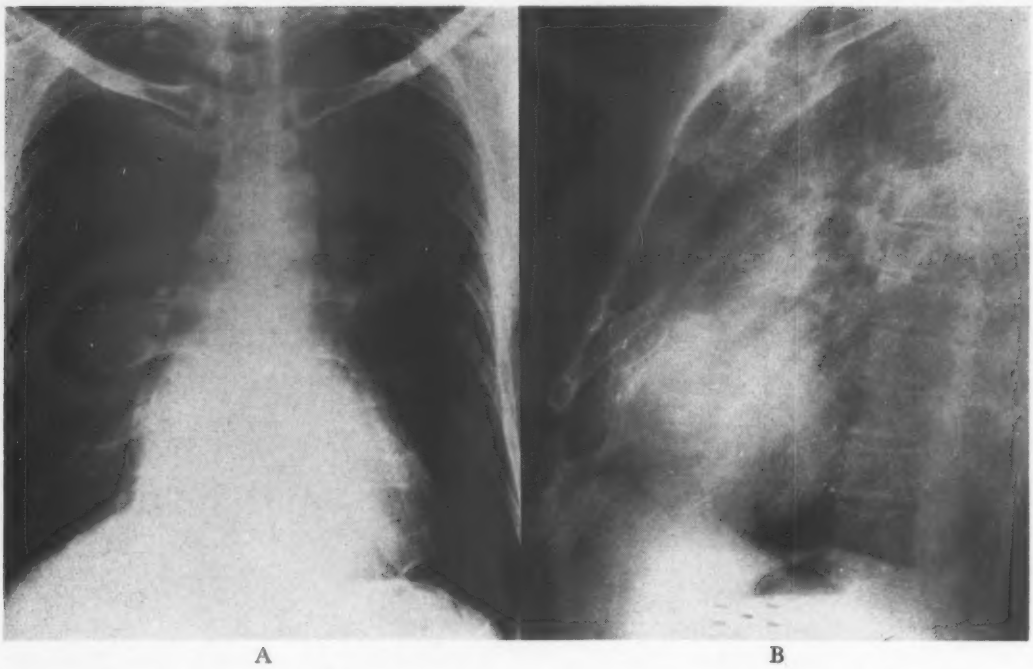
mm. Hg and a roentgenogram of the chest showed a more normal contour of the left cardiac border.

CASE 6. W. C., a 49 year old man, was admitted to the Methodist Hospital on November 2, 1958 with the diagnosis of massive left ventricular aneurysm. Three months previously he had experienced severe substernal pain due to coronary occlusion. Following this he was completely incapacitated, experiencing dyspnea with minimal exertion and occasional angina. Subsequent roentgenograms of the chest revealed a ventricular aneurysm (Fig. 7).

On admission the blood pressure was 110/75 mm. Hg with associated marked cardiomegaly. The electrocardiogram demonstrated extensive anterior infarction of indeterminate age with persistent S-T segment elevation (Fig. 8).

Cardiac catheterization revealed pulmonary hypertension following exercise (60/20) with a diminished cardiac index (1.36 L.). On fluoroscopy paradoxical motion of the aneurysm could be demonstrated.

Operation was performed on November 6, 1958. On incising the pericardium, extreme dilatation of the heart ensued apparently due to loss of pericardial support of the aneurysm, and cardiac arrest occurred.



A B

FIG. 9. Case 6. Roentgenograms of chest 4 months after operation showing reduction in cardiac size and normal configuration. A, posteroanterior view. B, left oblique view.

The nonpulsatile sac was supported manually and massage restored a feeble cardiac action. Cannulation of the venae cavae via the right common femoral vein was hastily performed in the right side of the groin for venous outflow and the right femoral artery was cannulated for return of oxygenated blood. With support from the pump oxygenator to improve coronary flow, vigorous cardiac action returned permitting successful excision of the aneurysm. A large quantity of thrombus was removed with the specimen of aneurysm, yet no embolic phenomena appeared after operation. The patient made an uneventful recovery and left the hospital 21 days later.

Follow-up Study: Four months after operation he was receiving only a maintenance dose of digitalis and experienced minimal dyspnea on exertion. Roentgenograms of the chest showed a striking reduction in heart size and improvement in the cardiac configuration (Fig. 9).

CASE 7. L. J., a 63 year old man, was admitted to the Veterans Administration Hospital on April 28, 1959. He had an anterolateral myocardial infarction on October 1, 1958. He was psychotic and walked during the first 4 days of his immediate postinfarction period. In January 1959 and in April 1959, he had separate hospital admissions for exertional shortness of breath, angina and marked fatigability. He continued to take digitalis and diuretics.

Physical examination revealed an emaciated, chronically ill, Negro man with left ventricular hypertrophy and a "roll out" phenomenon, a gallop rhythm and evidence of left and right heart failure. Blood pressure was 110/80 mm. Hg. The electrocardiogram revealed anterolateral myocardial infarction with S-T segment elevation in leads V_2 through V_6. Roentgenographic studies revealed a large left ventricle with aneurysm formation and secondary pulmonary congestion (Fig. 10).

Cardiac catheterization studies revealed severe pulmonary hypertension (64/30) and reduced cardiac indices both at rest and with exercise (Table I).

Operation was performed on April 30, 1959 and the aneurysm was excised. The patient died some 2 hours postoperatively, the myocardium failing to make a satisfactory recovery following surgery.

CASE 8. A. L., a 63 year old man, was admitted to St. Luke's Hospital on May 3, 1959 with a history of exertional dyspnea, cough and angina following an acute anterior myocardial infarction on March 4, 1959. In early April 1959, the patient had a bout of chills and fever up to 104°F. Presumptive diagnosis was mural bacterial endocarditis, which was treated with antibiotics.

On examination, the blood pressure was 70/40 mm. Hg, the heart sounds were very distant, the heart was enlarged to the left. The electrocardiogram revealed anterior myocardial infarction with Q waves and persistent S-T elevation in leads V_1 through V_4. Teleoroentgenograms revealed a markedly enlarged left ventricle with an aneurysmal bulge located in the left lateral aspect of the left ventricle. Cardiac catheterization was not performed.

Operation was performed on May 8, 1959, using complete cardiopulmonary bypass. The aneurysm measured 8 cm. in diameter and was located in the

FIG. 10. Case 7. Roentgenogram reveals a large left ventricular aneurysm and pulmonary congestion.

lateral surface of the left ventricle. It was excised completely and found to be filled with adherent thrombi. The patient died suddenly 10 days later, apparently of a rhythm disturbance.

Autopsy revealed an old atheromatous occlusion of the anterior descending branch of the left coronary artery and partial occlusion of the right coronary artery by hemorrhage into an atheroma. A healing surgical wound in the wall of the left ventricle was noted with the suture already covered by epithelium.

CASE 9. W. K., a 63 year old man, who was known to have hypertension since 1936, was admitted to Methodist Hospital on May 19, 1959, with congestive heart failure. In March 1958, the patient had an anterolateral myocardial infarction. In September 1958, aneurysm of the left ventricle was first discovered and at that time the patient had left ventricular failure and marked fatigability. A second coronary occlusion occurred on March 11, 1959, with subsequent development of ventricular tachycardia and congestive failure.

Physical examination revealed an enlarged heart with a gallop rhythm and runs of ventricular tachycardia and evidence of combined left and right heart failure. The electrocardiogram revealed anterolateral myocardial infarction with elevated S-T segments in V_2 through V_6, and runs of ventricular tachycardia. Roentgenograms revealed an aneurysm involving the apical and posterolateral surface of the left ventricle. *Cardiac catheterization* revealed moderate pulmonary hypertension (47/18) and reduced resting cardiac index (1.2 L.) with some increase on exercise (Table 1).

Operation was performed on June 2, 1959, and the aneurysm was successfully resected employing the cardiopulmonary bypass. At present, in March 1961, the patient is retired but active and has no evidence of failure or angina. Roentgenograms have shown marked reduction in the cardiac size.

CASE 10. H. S., a 49 year old man, was admitted to Methodist Hospital on July 17, 1959, having had an anterior infarction initially in 1955 with a subsequent excellent recovery. In January 1959, a second infarction occurred. In May 1959, left ventricular failure occurred and right heart failure developed in June 1959.

Physical examination revealed a chronically ill patient with an enlarged heart, diastolic gallop rhythm and evidence of combined left and right heart failure. The electrocardiograms revealed anterior infarction with persistent S-T segment elevation in leads V_3 through V_6, and anterolateral periinfarction block. Teleoroentgenograms revealed an enlarged heart with an aneurysmal bulge of the left ventricle laterally and posteriorly. Fluoroscopy demonstrated a paradoxical pulsation in this area.

Cardiac catheterization revealed moderately elevated pulmonary arterial pressures (Table 1). Cardiac output was not determined because of the patient's critical condition at the time.

Operation was performed on July 24, 1959, and a large ventricular aneurysm located in the anterolateral surface of the left ventricle was resected using the cardiopulmonary bypass technic.

Recent follow-up study, in March 1961, revealed the patient to be active and working as an accountant, without any angina and with no evidence of congestive heart failure. There was marked reduction in size of the cardiac silhouette with complete disappearance of the aneurysm. No essential change in electrocardiogram was noted.

CASE 11. T. G., a 55 year old man, was admitted to Methodist Hospital on August 2, 1959, having sustained an acute anterior infarction on October 18, 1958. He had continued to be active for 4 days after the onset of the infarction. In December 1958, pulmonary congestion and fatigability developed, persisting intermittently until the time of admission. In January 1959, roentgenologic examination revealed the presence of a left ventricular aneurysm.

Physical examination revealed an enlarged heart to the midaxillary line, a "roll out" phenomenon, a gallop rhythm and evidence of combined right and left heart failure. Blood pressure was 100/65 mm. Hg. The electrocardiogram revealed an anterior infarction with elevated S-T segments in V_1 through V_6 (Fig. 11). Roentgen examination revealed an enlarged left ventricle with an aneurysmal bulge in its lateral and posterior aspects. *Cardiac catheterization* revealed severe pulmonary hypertension (54/20) (Table 1).

At operation on August 6, 1959, an 8 cm. aneurysm was resected involving the anterior and lateral walls of the left ventricle. It was filled with clots. *At*

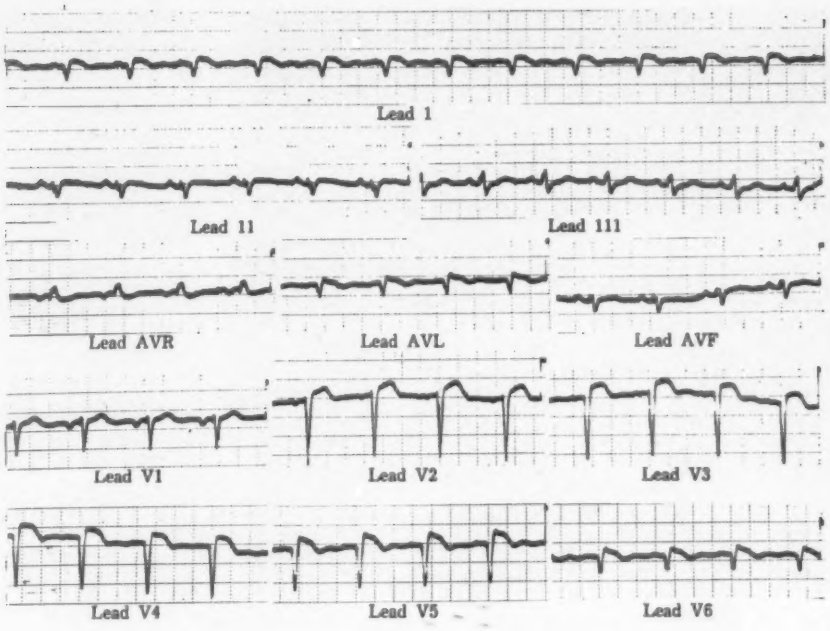


FIG. 11. Case 11. Electrocardiogram reveals evidence of an anterior myocardial infarction. There is significant diffuse S-T segment elevation as might be associated with a ventricular aneurysm.

follow-up study in February 1961, the patient was found to be free of angina and there was no evidence of congestive heart failure. The patient has returned to full time work and the cardiac silhouette has markedly decreased in size.

CASE 12. L. K., a 57 year old man, was admitted to Methodist Hospital on September 27, 1959, having had an anterior and diaphragmatic infarction 10 weeks previous to admission. Four weeks prior to admission exertional dyspnea and fatigability developed.

Physical examination revealed an enlarged heart with a "roll out" phenomenon on the left, gallop rhythm, and evidence of pulmonary edema. Blood pressure was 140/65. The electrocardiogram revealed anterior and diaphragmatic infarction with Q waves and S-T segment elevation in leads V_2 through V_6 (Fig. 12).

Teleroentgenograms revealed an enlarged heart with a ventricular aneurysm in the left lateral portion with a paradoxical pulsation noted on fluoroscopy.

Cardiac catheterization revealed severe pulmonary hypertension (65/25) and a reduced resting cardiac index (1.4 L.) (Table I).

At operation on October 6, 1959, an 8 cm. in diameter aneurysm involving the lower portion of the anterior surface of the left ventricle extending over into the diaphragmatic surface was excised by the cardiopulmonary bypass technic.

Follow-up examination on March 15, 1961 revealed no evidence of cardiac failure, á decrease in cardiac size and an active patient now working half time.

CASE 13. G. D., a 54 year old man, was admitted to Methodist Hospital on September 28, 1959, having had a myocardial infarction in March 1959. Intermittent bouts of pulmonary edema had occurred since then despite the use of digitalis, diuretics and a low salt diet, and in early September 1959, a possible left renal embolus had occurred. An aneurysm of the left ventricle had first been discovered by routine x-ray film in July 1959.

Physical examination revealed evidence of a grossly enlarged heart, a gallop rhythm and combined left and right cardiac decompensation. Blood pressure was 145/95 mm. Hg. The electrocardiogram revealed evidence of an anterodiaphragmatic infarction with S-T segment elevation and Q waves in leads V_2 through V_6. Teleroentgenograms revealed a diffusely enlarged left ventricle with relatively feeble paradoxical pulsations on the left heart border between the cardiac apex and the region of the left atrial appendage. *Cardiac catheterization* revealed severe pulmonary hypertension (60/30) and reduced cardiac indices at rest and with exercise (Table I).

Operation was performed on October 8, 1959, and a wedge resection of the ventricular aneurysm was done employing the cardiopulmonary bypass technic. The patient was discharged on the nineteenth postoperative day, compensated. *A recent follow-up* examination in March 1960 revealed an active subject who is maintaining satisfactory compensation.

CASE 14. V. F., a 61 year old white man, was admitted to Methodist Hospital on November 3, 1959, having sustained a myocardial infarction in 1953. An aneurysm producing congestive heart failure was resected in April 1954, in Philaldelphia by Dr. C. P. Bailey, employing the tangential excision technic with a special clamp. There was improvement following this operation but for the past several months prior to admission the patient had refractory orthopnea, dyspnea and fatigability in spite of therapy with digitalis, diuretics and a low salt diet.

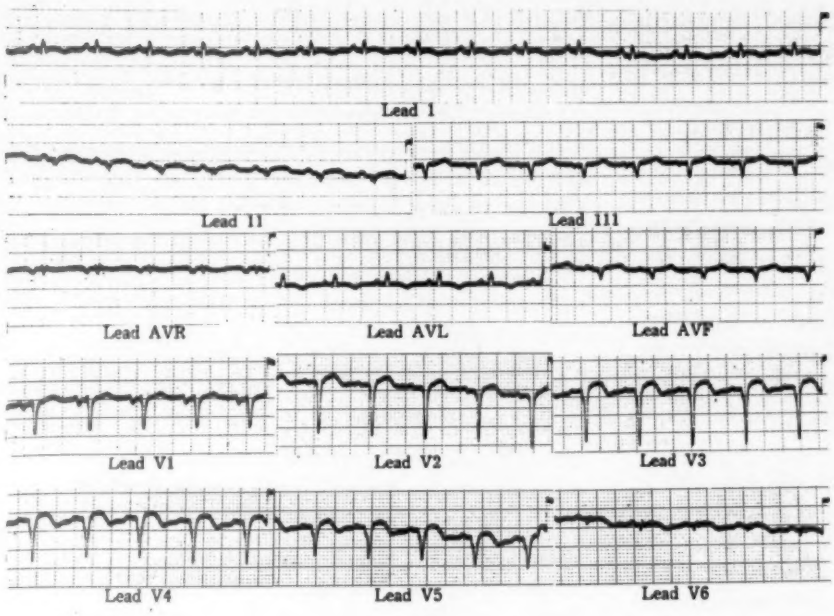


FIG. 12. Case 12. Electrogram reveals an anterodiaphragmatic infarction, age indeterminate, but with S-T elevation compatible with a ventricular aneurysm.

Physical examination revealed a diffuse "roll out" phenomenon of the left ventricle with enlargement of the heart to the anterior axillary line. The heart sounds were faint and a distant gallop rhythm was present. An apical grade 2 systolic murmur was heard and pulmonary edema existed. The electrocardiogram revealed an anterior infarction with persistent S-T segment elevation in leads V_1 through V_4 and an anterolateral periinfarction block. Roentgen studies revealed combined enlargement of the heart with an irregular left heart border and an aneurysmal bulge in the lateral and anterior border of the left ventricle with associated paradoxical motion. *Cardiac catheterization studies* revealed severe pulmonary hypertension (80/31) and markedly reduced cardiac index (1.3 L.) (Table 1). Exercise tests were not performed.

At operation on November 5, 1959, a recurrent aneurysm of the wall of the left ventricle was noted, extending superiorly to the region of the pulmonary outflow and inferiorly to the tip of the ventricle. Marked thickening and fibrosis of the area and evidence of old sutures with scars were seen. The aneurysm was resected successfully, but at the end of the procedure a dissection of the thoracic aorta suddenly developed, extending down to the bifurcation of the aorta to the femoral arteries, and the patient died.

Clinical Features

Patients with myocardial infarctions in whom aneurysms develop may die within a few days of the acute infarction, or may live but continue to have symptoms such as anginal attacks, repeated episodes of arrhythmias, myocardial infarctions and congestive heart failure. In our fourteen cases of myocardial aneurysm, preoperative symptoms were as follows: All fourteen patients had exertional dyspnea and left heart failure; eleven were easily fatigued; ten had angina; five had right heart failure; four had rhythm disturbance and one had emboli. In about half the patients there is a quiescent interim period free of symptoms between the formation of the aneurysm and the final illness. This period may be weeks, months, or even years.

SYMPTOMS

There are no symptoms pathognomonic of ventricular aneurysm. Ventricular aneurysms may be noted in a patient completely free of cardiac symptoms. In most patients the symptoms are predominantly those of a poorly functioning left ventricle. The inelastic noncontractile sac behaves much like the left atrium in mitral insufficiency; part of each left ventricular stroke volume is dissipated in filling the sac. Weakness was noted in over half of our patients. Exertional shortness of breath, orthopnea and extreme fatigability were very common. Repetitive bouts of tachycardia were encountered in three patients. There may be supraventricular disturbances such as atrial fibrillation, flutter or tachycardia, or ventricular tachycardia. Symptoms of right heart failure were noted in the advanced cases. Angina was present in over half of the cases and in several it was quite severe. Renal emboli occurred in one of our patients; however, thromboembolic phenomena may be frequent for the ventricular

sac acts as a nidus where blood clots, lamination and even calcification may occur.

PHYSICAL FINDINGS

Enlargement of the cardiac dulness was present in thirteen out of fourteen patients. In our fourteen cases of ventricular aneurysm, preoperative physical findings were as follows: All fourteen patients had sinus rhythm and were normotensive; thirteen had cardiac enlargement; eleven had gallop rhythm and distant heart sounds; seven had diffuse pulsation laterally; two had apical systolic murmur and systolic murmur in one patient was basilar. In some a forceful, diffuse or heaving apical impulse was seen. In others a separate pulsation independent of the apical impulse, the so-called "roll out" phenomenon, which may be medial and above the apex beat, has been noted. In all but one of our patients a gallop rhythm was heard. Sinus rhythm was present in all patients. Murmurs were heard in only three of our fourteen patients; all were systolic in time, two being apical and one in the aortic area. No diastolic murmurs were heard. In Moyer and Hiller's series,[25] five of nineteen patients had a systolic murmur and one had a diastolic murmur. Most authors agree that murmurs offer little in the way of diagnostic aid in ventricular aneurysms. The usual accompanying signs of left ventricular failure may be present and in the more severe cases evidence of right-sided decompensation may also become evident.

ELECTROCARDIOGRAPHIC FINDINGS

The most common electrocardiographic pattern encountered was that of a previous myocardial infarction; namely, deep Q waves and persistence of the S-T segment elevation or depression, depending on the site of the original injury. In all fourteen of our patients the presence of S-T segment elevation was noted. Anterior myocardial aneurysms gave rise to S-T segment elevation in V_1 through V_4, and anterolateral aneurysms to elevation in V_3 through V_6. Posterior (diaphragmatic) aneurysms revealed depression of some of the precordial S-T segments and elevation of the S-T segments in leads II, III and aVF. A combined anterior and diaphragmatic aneurysm was seen in two cases.

Moyer and Hiller[25] accounted for the S-T segment elevation by two factors, namely, lack of modifying potential from completely infarcted muscle and hypertrophy of the opposite ventricular wall. They further stressed that failure to verify the presence of an extensive infarction pattern on electrocardiographic tracings in the presence of an abnormal bulge in the cardiac silhouette by roentgen studies does not exclude but should cast serious doubt on the diagnosis of cardiac aneurysm, and on the basis of our operative experiences we would agree with this observation.

ROENTGEN FINDINGS

Standard posteroanterior, right anterior oblique and left anterior oblique teleoroentgenography may reveal enlargement of the left ventricle with deformity of its contour, localized protuberance inseparable from the cardiac silhouette, bulging of the anterior or posterior border of the heart, or increased density or calcification of the ventricular wall. Fluoroscopy may further delineate abnormal or absent pulsations in the aneurysms. In the majority the pulsation of the ventricular aneurysm is asynchronous or contrapulsile, bulging outward when the remainder of the ventricle contracts. However, expansile pulsations may be absent when the wall of the sac is reinforced by a thrombus from within and a thickened adherent pericardium from without, or when the wall is calcified, little pulsation can be expected. In calcified aneurysms the calcific shadow is linear and even, is situated within the heart border and is limited to the left ventricle, unlike the calcified pericardium of constrictive pericarditis. Calcification of a valve can be differentiated by the shape and position of the shadows.

Angiocardiography: Visualization of the aneurysm by contrast media is frequently helpful. Dolly, Dotter and Steinberg[26] have employed iodopyracet (Diodrast®) for this purpose. In our experience the injection of 40 cc. of 90 per cent Hypaque® (diatrizoate sodium) into the pulmonary artery with a mechanical injector has produced satisfactory visualization. Chapman[27] has employed a similar technic in conjunction with the use of cineangiofluorography with excellent results. The latter technic has been employed in one patient in this series with good visualization of the aneurysm. Left ventricular puncture[28] with the injection of 40 cc. of radiopaque material has also demonstrated the aneurysm well, but we have not used this technic to date.

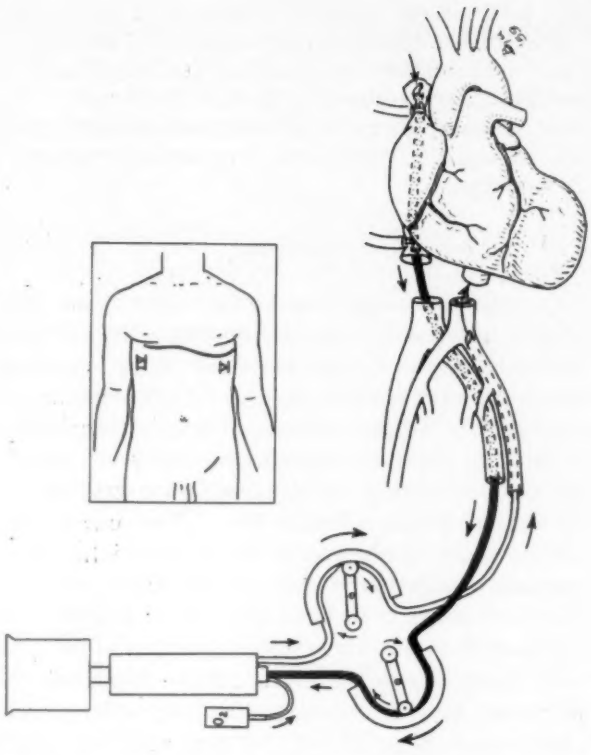


FIG. 13. Drawing showing method of surgical excision of left ventricular aneurysm utilizing pump oxygenator for temporary cardiopulmonary bypass. Technic of introduction of catheters in femoral artery and vein permits complete cannulation through the groin. Inset shows surgical incision used for optimum exposure through left fifth and right fourth intercostal spaces.

CARDIAC CATHETERIZATION

In twelve of fourteen patients cardiac catheterization was done preoperatively (Table 1). The cardiac outputs were reduced in all; the average cardiac index was 1.5 L. per minute per M^2 of body surface. Assuming an average normal cardiac index of approximately 2.2 L. per minute per M^2, the average reduction in left ventricular output in this series was 33 per cent. Two patients (Cases 2 and 3) showed an increase in resting output postoperatively and in both a substantial increase in cardiac output occurred after moderate exercise. In Case 5 there was no change in cardiac output after operation but this may have been influenced by certain technical difficulties during catheterization. Pulmonary hypertension was present in eleven of twelve patients catheterized preoperatively and in one of these (Case 6) it was present only during exercise. In the three cases studied postoperatively, pulmonary pressures have returned to normal levels in the resting state (Cases 2, 3 and 5). Not all patients who were catheterized before operation were studied under the stress of exercise because of the appearance of angina and other disturbing symptoms.

SURGICAL TECHNIC

Bypass Procedure: In all fourteen patients excision of the ventricular aneurysm was performed using a pump oxygenator for temporary cardiopulmonary bypass (Fig. 13). A stainless steel oxygenator based upon the bubble diffusion principle was used.[29] DeBakey roller pumps of the complete occlusion type were used to withdraw venous blood from the venae cavae and to return oxygenated blood to the systemic arterial system. Venous cannulation of the venae cavae was performed in all instances by passing a 9/32 inch diameter plastic tubing into the superior vena cava through the right common femoral vein. By placing the perforations at the proper point to drain the superior and inferior venae cavae, cardiac inflow occlusion was obtained by tape ligatures. Cannulation of the arterial system was performed using a 3/16 inch diameter plastic catheter inserted into the common femoral artery. Thus, all cannulations were performed in most instances before cardiac manipulations or even pericardiotomy. The advantage of this technic was clearly demonstrated in Case 6 in which acute cardiac dilatation and arrest occurred immediately upon opening the pericardium. While an assistant massaged the heart, the necessary cannulations through femoral vessels were performed and the bypass was started. Upon restoration of adequate systemic flow cardiac resuscitation was promptly accomplished.

Blood for priming the system was collected on the day preceding operation into siliconized glass bottles containing 25 mg. of heparin.[30] Just prior to bypass the patient received heparin, 1.5 mg. per kg. body weight, and immediately following bypass the heparin was neutralized with protamine sulfate (Polybrene®) 3 mg. per kg. body weight. Rates of perfusion varied from 35 to 50 cc. per minute per kg. body weight but in no instance did total flow exceed 3000 cc. per minute. Induced cardiac arrest was not used in any case but in all cases intermittent occlusion of the ascending aorta was used to reduce the volume of return through the coronary sinus. Blood entering the left ventricle was aspirated and collected in a reservoir containing stainless steel sponges coated with Dow-Corning antifoam A substance. Wherever necessary this blood was returned to the pump oxygenator system.

Operative Technics: An anterior thoracotomy incision entering the left fifth intercostal space and the right fourth space was made transecting the sternum with a Gigli saw (Fig. 13). A sternal retractor was inserted and the heart was exposed. The common femoral artery and vein were mobilized through a short incision in the groin and cannulations were performed after heparinization. Tape tour-

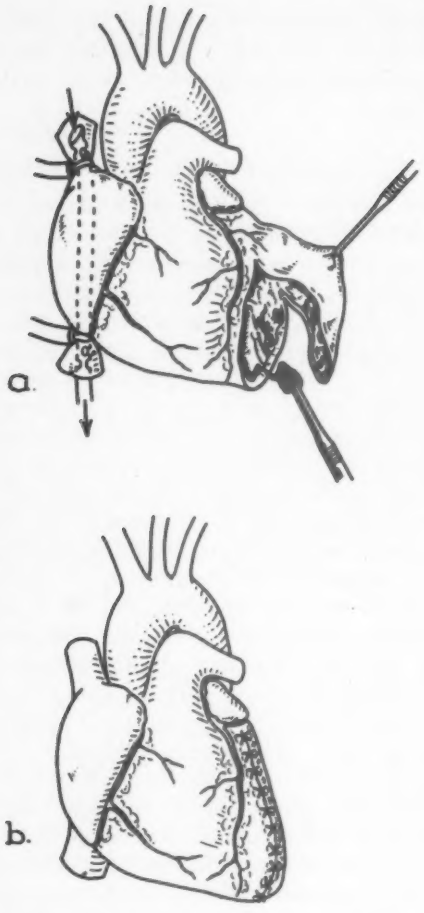


FIG. 14. Drawing showing technic of excision and ventriculorrhaphy for ventricular aneurysm. A, the aneurysm is excised and thrombi are removed. B, the ventricular defect is repaired with continuous and interrupted sutures of black silk.

niquets were passed about the superior and inferior venae cavae. With the pump oxygenator functioning and the venae cavae occluded the adherent pericardium was carefully dissected off the underlying aneurysm. An incision was made in the apex of the aneursym and the lesion was opened widely. Thrombi were removed and the junction of the aneurysm and relatively normal myocardium was identified (Fig. 14). The aneurysm was excised, care being taken not to compromise the size of the reconstructed left ventricle by too extensive removal. Papillary muscles and the mitral valve were carefully identified and preserved. In most instances the aneurysm was excised through tissue which was fibrous or cicatricial rather than muscular to prevent sutures from cutting through and to facilitate closure. The ventricular repair was done with continuous 2-0 and 3-0 black silk sutures. This suture was reinforced with interrupted sutures of silk.

As the ventriculotomy was closed, the left ventricle was permitted to fill with blood to force out the air and in no instance was air embolism a problem. The pericardium was closed tightly over the suture line in the ventricle but was loosely closed elsewhere. After the cannulae were removed the femoral artery and vein were repaired with fine silk sutures. In most instances the period of complete cardiac bypass was less than 12 minutes and in no instance exceeded 20 minutes.

COMMENTS

In patients with ventricular aneurysm following myocardial occlusion the effect of the noncontractile aneurysmal sac upon cardiac function may be measured by right heart catheterization. Stroke volume of the left ventricle at rest is reduced because the force of contraction of the remaining uninvolved myocardium is dissipated in the flaccid sac. This effect becomes more evident during exercise when the normally anticipated increase in cardiac output does not occur. Indeed, exercise of the patient appears to cause an actual reduction of output indicating that the remaining myocardium fatigued quickly because of the unfavorable circumstances produced by the noncontractile aneurysm. During exercise stasis in the left atrium and pulmonary circuit occurs and is manifested by increased pulmonary capillary and pulmonary arterial pressures. This undoubtedly accounts for the immediate onset of dyspnea on exertion and the tendency for patients to develop pulmonary congestion.

In twelve of our patients cardiac catheterizations were performed before operation and marked reduction in cardiac output was found. In three of the four patients who had cardiac catheterizations postoperatively, there were increases in the cardiac output. Similarly, a lower resting pulmonary arterial pressure within normal limits was noted after operation. We encountered three deaths; one patient died of increasing failure about 2 hours after the operation, one died of a dissecting aneurysm of the thoracic aorta at the time of operation, and one probably of a rhythm disturbance 10 days postoperatively, just as he was ready to be discharged from the hospital. In this subject at necropsy the suture lines were well healed and the left ventricle was intact and apparently had functioned satisfactorily. Clinically, the disappearance of fatigue, left ventricular failure and angina, and the general feeling of well being was very noticeable in the other eleven patients. All have increased their activity greatly, and seven are working full time, one part time, and the other three, although retired, remain active.

Teleoroentgenograms have demonstrated rather striking reduction in the cardiac size; however, relatively little change in the postoperative electrocardiograms has been noted.

Summary

Ventricular aneurysm is a frequent late complication of extensive myocardial infarction. Although cardiac rupture is rare, serious and frequently incapacitating symptoms result from the impairment of cardiac function produced by the noncontractile, expansile aneurysm. Embolism from mural thrombi may also produce disastrous complications.

Fourteen patients with aneurysm of the left ventricle following myocardial infarction have been treated by surgical excision of the aneurysm utilizing an extracorporeal pump oxygenator for temporary cardiopulmonary bypass, with three deaths. Cardiac catheterization studies performed prior to surgery in twelve of these patients revealed a reduction in cardiac output and significant pulmonary hypertension. After operation cardiac function improved and the eleven survivors received clinical benefits.

The optimum time for surgical intervention following myocardial infarction is probably governed by the pathologic state of the diseased myocardium. At 3 months fibrous tissue develops at the margin of the aneurysm and firm repair of the ventricle after aneurysmectomy is facilitated.

Surgical excision and ventricular repair is a feasible and rational surgical treatment for ventricular aneurysm following myocardial infarction when the lesion is of sufficient size to cause impairment of cardiac function.

Addendum

A total of twenty-four patients in our series have had a resection of a ventricular aneurysm. There have been nineteen survivors. Of the deaths occurring, four were of subjects over 60 years of age.

References

1. Appelbaum, E. and Nicolson, G. H. B. Occlusive diseases of the coronary arteries; an analysis of the pathological anatomy in 168 cases with electrocardiographic correlation in 36 of these. *Am. Heart J.*, 10: 662, 1935.
2. Bean, W. B. Infarction of the heart. III. Clinical course and morphological findings. *Ann. Int. Med.*, 12: 71, 1938.
3. Schlichter, J., Hellerstein, H. K. and Katz, L. N. Aneurysm of the heart: a correlative study of 102 proved cases. *Medicine*, 33: 43, 1954.
4. Wang, C. H., Bland, E. F. and White, P. D. A note on coronary occlusion and myocardial infarction found post mortem at the Massachusetts General Hospital during the twenty year period from 1926 to 1945 inclusive. *Ann. Int. Med.*, 29: 601, 1948.
5. Sternberg, M. Das chronische partielle Herzaneurysmia, p. 46. Vienna and Leipzig, 1914. Franz Deutlicke.
6. Baillow. Cited in reference 15.
7. Barrich, O. Cited in reference 3.
8. Dionis, P. Anatomia corporis humani, juxta circulationem sanguines et recentiores observationes. Geneva, 1696. Cramer and Perachon.
9. Galeati, D. G. De bononiensi scientiarum et atrium instituto atque academia commentarii. *De morbis duobus*, 4: 26, 1767.
10. Hunter, J. An account of the dissection of morbid bodies. Original manuscript in the library of the College of Surgeons, No. 32, pp. 30–32, 1757.
11. Cruveilhier, J. Essai sur l'anatomie pathologique en général, el sur les transformations et productiones organiques en particulier. Paris, 1816. Vol. 1, p. 60. Chez l'auteur. *Nouvelle bibliothéque. méd.*, 2: 72, 1827.
12. Cohnheim, J. and Schulthess-Rechberg, A. V. Ueber die Folsen der Kranzarterienverschliessung fur das Herz. *Arch. path. Anat.*, 85: 503, 1881.
13. Sézary, A. and Alibert, J. Aneurysm in wall of heart. *Bull et. mém. Soc. méd. hôp. Paris*, 46: 172, 1922.
14. Parkinson, J., Bedford, D. E., and Thomson, W. A. R. Cardiac aneurysm. *Quart. J. Med.*, 7: 455, 1938.
15. Crawford, J. H. Aneurysm of the heart. *Arch. Int. Med.*, 71: 502, 1943.
16. Hanbury, W. J. Calcified cardiac aneurysm. *Brit. Heart J.*, 19: 435, 1957.
17. Master, A. M., Jaffe, H. L., Teich, E. M. and Brinberg, L. Survival and rehabilitation after coronary occlusion. *J.A.M.A.*, 156: 1552, 1954.
18. De Camp, P. T. Excision of an aneurysm of the left ventricle. *Ochsner Clin. Rep.*, 2: 38, 1956.
19. Beck, C. S. Operation for aneurysm of the heart. *Ann. Surg.*, 120: 34, 1944.
20. Murray, G. The pathophysiology of the cause of death from coronary thrombosis. *Ann. Surg.*, 126: 523, 1947.
21. Bailey, C. P., Bolton, H. E., Nichols, H. and Gilman, R. A. Ventriculoplasty for cardiac aneurysm. *J. Thoracic Surg.*, 35: 37, 1958.
22. Likoff, W. and Bailey, C. P. Ventriculoplasty: excision of myocardial aneurysm. *J.A.M.A.*, 158: 915, 1955.
23. Cooley, D. A., Henly, W. S., Amad, K. H. and Chapman, D. W. Ventricular aneurysm following myocardial infarction: results of surgical treatment. *Ann. Surg.*, 150: 595, 1959.
24. Lillehei, C. W. Personal communication.
25. Moyer, J. H. and Hiller, G. Cardiac aneurysms: clinical and electrocardiographic analysis. *Am. Heart J.*, 41: 3401, 1951.
26. Dolly, C. H., Dotter, C. T. and Steinberg, H. Ventricular aneurysm in a 29-year-old man studied angiocardiographically. *Am. Heart J.*, 42: 894, 1951.
27. Chapman, C. Personal communication.

28. Lehman, J. S., Musser, B. J. and Lyken, H. P. Cardiac ventriculography. *Am. J. Roentgenol.*, 77: 207, 1957.
29. Cooley, W. A. Belmante, B. A., Zeis, L. P. and Schnur, S. Surgical repair of ruptured interventricular septum following acute myocardial infarction. *Surgery*, 41: 930, 1957.
30. Abbott, J. P., Cooley, D. A., DeBakey, M. E. and Ragland, J. E. Storage of blood for open heart operations. *Surgery*, 44: 698, 1958.

Experimental Study

Phenol-Talc Procedure for Myocardial Revascularization

Experimental and Clinical Studies*

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TWENTY-SIX years ago the first experimental method for improving the blood supply to the heart was presented by Beck and Tichy.[1] Their procedure consisted of mechanical abrasion of the epicardium ("epicardiectomy") and the placing of neighboring tissues on the abraded heart. Beck demonstrated that this resulted in extensive anastomoses between the coronary arteries and those of the pericardium and mediastinum via vascularized adhesions. The effectiveness of these surgically-induced collateral vessels on the myocardial blood supply was demonstrated by the survival of dogs having almost total occlusion of both coronary arteries. Later in 1935, Beck[2] presented the first clinical case treated by the method.

The production of epicardial-pericardial adhesions by the use of intrapericardial talc was described by Thompson[3] in 1939. There was active bleeding from these adhesions and histologic examination revealed the presence of new blood vessels. In 1942, Thompson and Raisbeck[4] presented a series of clinical cases treated by a talc-induced adhesive pericarditis and stated that all patients so treated had symptomatic relief and an increase in exercise tolerance. Schildt, Stanton and Beck[5] in 1943 discussed the effects of various irritants, including talc, on the heart and stated that all had harmful side effects or were not as effective as asbestos, which Beck[6] continued to use.

Chemical debridement of the epicardium rather than its mechanical abrasion was proposed by Harken et al.[7] in 1955. For this purpose, they applied 95 per cent phenol to the heart, believing that this modification, by more effectively removing the epicardial barrier, promoted a greater growth of new vessels large enough to carry the Schlesinger mass from pericardium to myocardium.

Numerous other procedures have been designed to promote myocardial revascularization. Their proponents have demonstrated experimentally the value of these procedures as effective means of bringing new blood to the heart and/or causing the development or enhancement of already existing intercoronary anastomoses. An extensive review of these procedures has been made by Vansant and Muller.[8]

Several of these procedures have been used clinically with reported success.[9–11] However, it is noteworthy that clinical assessment leaves much to be desired because so much of the assessment is subjective in nature; indeed, sham internal mammary artery ligations have been demonstrated clinically to be beneficial.[12] Thus one of us[13] has stated: "The greatest present need is the development of a precise test to measure coronary arterial blood flow in the human."

In the experimental animal, however, a variety of methods have been utilized for determining the effectiveness of revascularization procedures; the majority of these are indirect.

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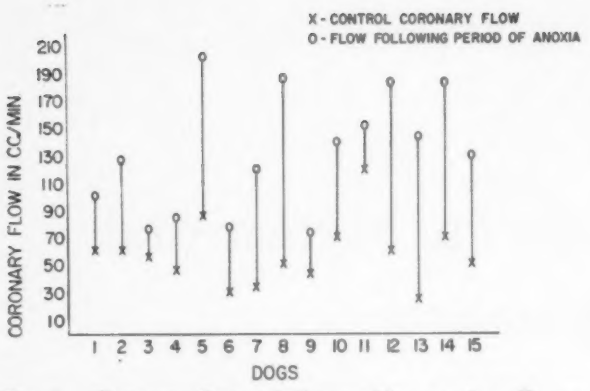

FIG. 1. Coronary flow as influenced by anoxia. From: Lord et al., *Surgery*, 43: 207, 1958.[14]

In our laboratory a method[14] has been developed for the direct measurement of the coronary blood flow in dogs. This method has given consistent results and has enabled us[15,16] to evaluate several revascularization procedures. Our method is not applicable to human subjects. For human beings, the ingenious method presented by Goldsmith and Mayer,[17] for evaluating myocardial blood supply by direct measurement of myocardial temperature changes in response to injections of known doses of iced saline, or refined radioisotope technics[18] currently being investigated for measuring coronary blood flow, may soon provide this necessary information.

Allela and co-workers[19] have demonstrated that coronary blood flow is related to the degree of myocardial anoxia. Studies previously reported by us[14] have corroborated these findings and have demonstrated that temporary myocardial anoxia (4 to 7 minutes) will result in a coronary blood flow two and a half times greater than the control flow (Fig. 1). Furthermore, Zoll, Wessler and Schlesinger[20] showed that myocardial anoxia will promote the development of new vascular channels. Based on these reports we concluded that the production of a relative myocardial ischemia coincident with the revascularization procedure would enhance the effectiveness of the procedure by creating a demand for additional blood flow and thereby result in more significant information. Therefore, in this investigation of the phenol-talc cardiopexy, the method of Pearl, Joseph and Citret[21] involving the partial ligation of the anterior descending branch of the left coronary artery was used to produce a degree of myocardial anoxia. We have not performed pneumopexy in this series because previous study[15] has led us to conclude that addition of the lingula to the procedure did not contribute to the promotion of extracoronary blood flow.

METHOD

Three groups of mongrel dogs, weighing 11.5 to 19 kg., were prepared. *Group 1* was a control series of six dogs which had a routine thoracotomy and pericardiotomy performed. The pericardium and thorax were left open for at least 1 minute following which they were closed in the usual manner without drainage.

Group 2 was a series of seven dogs subjected to a routine left thoracotomy and pericardiotomy, followed by ligation of the anterior descending branch of the left coronary artery over a No. 22 gauge needle which was immediately removed. The pericardium and thorax were then closed in the usual manner without drainage.

Group 3 consisted of eleven dogs subjected to left thoracotomy and pericardiotomy followed by the application of 90 per cent phenol solution to the epicardium and inner surface of the pericardium, and the instillation of 1.5 gm. of talc U.S.P. (magnesium silicate) into the pericardial sac. Partial ligation of the anterior descending branch of the left coronary artery was performed as in group 2. The pericardium and thorax were then closed in the usual manner.

Following this initial operative procedure, a period of approximately 3 months was allowed to elapse before reoperation and measurement of the coronary blood flow.

A. Measurement of Coronary Blood Flow: At the end of this interval, the dogs were placed on cardiopulmonary bypass and studies of coronary blood flow were made by the method previously described by Lord et al.[14] and only briefly outlined here. Total extracorporeal perfusion utilizing two Sigmamotor pumps and a simple vertical nonhelical bubble oxygenator was employed. To prevent bronchial flow, returning via the pulmonary veins, from reaching the left side of the heart and subsequently the coronary ostia, both pulmonary hila were clamped. A Foley catheter, modified by ligating the tip of the catheter distal to the balloon and cutting three openings proximal to the balloon, was inserted through a small right ventriculotomy into the pulmonary artery. This catheter provided drainage for the return flow from the coronary sinus and Thebesian veins entering the right ventricle.

The venous return was collected in a graduate and several consecutive 30-second samples were taken, representing the total coronary blood flow. The aorta was then cross-clamped distal to the origin of the coronary ostia so that arterial blood from the extracorporeal unit could not reach the coronary arteries. The venous return was again collected for several consecutive 60-second intervals, representing the total *extracoronary* blood flow. All adhesions were then stripped in order to eliminate flow from any channels which had been produced by the experiment

and measurements were again taken of any residual flow. The mean of all measurements was then determined. The arithmetic difference between the average total extracoronary flow and the average flow following stripping was calculated. This value was assumed to represent the extracoronary blood flow resulting from the experimental procedure itself.

B. Adhesions: At the time of reoperation a gross assessment was made concerning the character and quantity of the adhesions present, and note taken regarding the production of bleeding upon lysis of adhesions.

C. Electrocardiographic Changes: The animals were monitored by the electrocardiogram during both operations. Lead II was used exclusively for photorecording because of technical factors. Tracings taken initially, following partial ligation of the coronary artery and at the time of reoperation were studied.

Results

A. Blood Flow (Table 1): In control dogs having had only a thoracotomy and pericardiotomy (group 1) the average extracoronary blood flow at the time of reoperation was 0.6 cc. per minute. The dogs upon which a partial ligation of the anterior descending branch of the left coronary artery was performed had an average extracoronary blood flow that was not remarkably different (0.3 cc. per minute). The average extracoronary blood flow in the dogs who had a phenol-talc cardiopexy coincident with partial ligation, was 4.3 cc. per minute. Ten of the eleven animals so treated had extracoronary blood flow in excess of 2 cc. per minute, although in no control dog was the flow greater than 1 cc. per minute.

The residual coronary blood flow following stripping of adhesions in the dogs in the group which had phenol-talc procedures was 1.5 cc. per minute. One might suppose that this value should correspond to the baseline flow found in control dogs (0.6 and 0.3 cc. per minute). We believe that the variance between these data can be explained on the basis that either (A) all adhesions were not effectively lysed or (B) the experimental procedure in some unknown manner acted to increase the baseline flow. We believe that the former is the more likely explanation because of the technical difficulties encountered in attempting to rapidly strip all the adhesions created (before fibrillation would occur). It is, therefore, quite possible that the actual flow resulting from the adhesions is even greater than the calculated one (2.5 cc. per minute).

It is interesting to note that if dog 1837 were omitted from the mean figures, by virtue of the wide disparity of its blood flow from other dogs, the total coronary blood flow for the experimental group (94 cc. per minute) would not be very different from controls (89 cc. per minute and 77 cc. per minute). The extracoronary blood flow figures would be even greater for the experimental procedure (4.6 cc. per minute).

B. Adhesions: At the time of reoperation, the majority of the control dogs as well as the dogs having had only partial ligation without cardiopexy, had an essentially benign pericardial sac, although in both groups a few had thin, fibrinous pericardial adhesions. All the dogs having had phenol-talc had a wealth of vascu-

Table 1
Measurements of Coronary Blood Flow

Group and Dog No.	Coronary Blood Flow (cc. per minute)			
	With Aorta Open	After Aorta Clamped	After Adhesions Stripped (residual flow)	Assumed due to Procedure (column 3 minus column 4)
Group 1 (Controls)				
898	42	0.6	...	...
1061	130	0.7	...	...
1135	186	0.0	...	...
1205	77	0.3	...	...
1326	48	0.7	...	...
1424	51	1.0	...	...
Average	*89*	*0.6*	...	...
Group 2 (Partial ligation only)				
1516	104	0.5	...	...
1605	76	0.3	...	...
1631	84	0.5	...	...
1650	72	0.6	...	...
1668	59	0.4	...	...
1700	56	0.0	...	...
1716	90	0.0	...	...
Average	*77*	*0.3*	...	...
Group 3 (Phenol-talc and partial ligation)				
1523	93	6.4	2.5	3.9
1592	109	3.3	2.8	0.5
1606	107	5.6	1.9	3.7
1607	107	7.6	...*	...
1626	70	3.0	0.7	2.3
1630	73	7.1	4.6	2.5
1665	107	3.4	0.2	3.2
1715	118	4.4	1.5	2.9
1747	66	3.2	0.2	3.0
1750	89	2.1	0.0	2.1
1837	225	1.1	0.0	1.1
Average	*106 (94)*†	*4.3 (4.6)*	*1.5 (1.6)*	*2.5 (2.8)*

* Drainage catheter became dislodged and measurements not obtained.

† Numbers in parentheses are averages excluding dog 1837.

larized myocardial-pericardial adhesions. These adhesions were frequently difficult to lyse and in most instances bled briskly upon being divided.

C. Electrocardiographic Changes: The electrocardiographic pattern as recorded from lead II showed in most instances the development of an inverted T wave, frequently accompanied by S-T segment shifts following partial coronary artery ligation. In some dogs, these changes had partially or completely reverted to normal by the end of the procedure.

We were unable to correlate the electrocardiographic pattern with the extracoronary blood flow at the time of reoperation. In most instances, however, the electrocardiographic pattern was within normal limits at that time.

DISCUSSION OF EXPERIMENTAL DATA

We have evaluated the phenol-talc procedure primarily by measurement of the extracoronary blood flow. Many other approaches have been used to study the collateral circulation which develops after revascularization. However, with the exception of the Mautz-Gregg backflow principle,[22] they are mainly indirect and do not provide information concerning the actual quantity of blood flowing through the newly formed collateral channels. Therefore, we believed that a method which measures the volume of blood entering the heart from extracoronary sources should be used. Kline[23] has stated: "The ultimate worth of the extramyocardial source will eventually be established on the basis of functional studies rather than on survival rates."

Relative Importance of Intercoronary and Extracardiac Collateral Anastomoses: With our method we are unable to determine the value of the revascularization procedure on the production or enhancement of intercoronary anastomoses. The presence of intercoronary anastomoses, by redistributing blood already available to the myocardium, is no doubt of great benefit in the prevention of myocardial infarction and angina. Leighninger[24] has stressed the value of these channels, particularly as related to the prevention of electrical instability and fibrillation giving rise to "mechanism death." Blumgart and Zoll[25] have demonstrated on autopsy specimens that the presence of intercoronary collaterals may explain the absence of clinical or pathologic evidence of myocardial damage despite the presence of longstanding obstructive arterial lesions. However, it would seem that the procedure of choice should be capable of effecting an ample extracoronary collateral circulation, in addition. It has been shown that myocardial anoxia will not only cause a large increase in coronary blood flow in the acute situation,[14,19,26] but also, over the long term, will in itself stimulate the production of new vascular channels.[20,27] Schlesinger,[28] using injection and dissection technics in the human heart, showed that "anastomoses develop readily whenever and wherever arteriosclerotic narrowing or occlusion causes obstruction to the coronary arterial circulation and are localized to the region where they are needed." Prinzmetal et al.,[29] using radioactive labeled red blood cells and perfusion of the coronary vessels with glass spheres, showed, moreover, that even the normal human heart has an extensive collateral circulation with anastomotic channels ready to function when the need arises. Thus, it would seem that the effectiveness of the procedure is of great importance in myocardial revascularization in producing an extracardiac collateral blood supply as well as intercoronary communications which will, indeed, form to some extent without surgical intervention.

Our method of measurement of coronary blood flow has been used to study several revascularization procedures and it has been our belief that adhesion-producing procedures have been the most valuable in this respect. Therefore, we elected to restudy the phenol-talc procedure under a situation of surgically-induced relative myocardial ischemia.

We believe that direct measurement of the coronary blood flow provides more information about the effectiveness of revascularization procedures than does any alternate means of evaluation. Other commonly used criteria such as size of infarcts and mortality rates, whether following acute coronary ligation, the insertion of thrombogenic wires into the coronary arteries,[30] the employment of Ameroid constrictors,[31,32] or the use of steel spring clips,[33] may be valuable indicators in the dog, but the information thereby obtained is not necessarily applicable to the human patient. These all require alterations of the dog's coronary vessels. It has been demonstrated, however, that there are normal variations in the coronary vasculature pattern in the dog[34,35] and that the canine heart and the human heart may differ anatomically.[36] It is for these reasons that results obtained by procedures necessitating such alterations may be misleading as clinical guides. Furthermore, Harken et al.[7] have pointed out

that 70% of normal dogs will die as a result of coronary artery challenge and the remarkable fact that 75% of "protected" animals will survive the same challenge regardless of which of the diverse "protective" procedures are employed. It is conceivable that the similarity in survival rates among these diverse procedures may be due to improved intercoronary communications or to the opening of intrinsic coronary collaterals rather than to an actual increase in blood supply. Thus, this means of determining the relative merit of revascularization procedures has limited value.

We have, therefore, performed partial coronary artery ligation, not for the purpose of promoting coronary occlusion, but rather to create a relative myocardial ischemia and thereby provide a stimulus for the ingrowth of new vessels. That myocardial ischemia is produced is demonstrated electrocardiographically by the appearance of inverted T waves and S-T segment changes following partial ligation.

The coronary blood flow measurements showed that the phenol-talc cardiopexy will bring to the heart an average of 4.3 cc. per minute of blood from extracardiac sources (4.1 per cent of total coronary blood flow) as compared with 0.3 cc. per minute (0.4 per cent) in dogs with partial ligation alone and 0.6 cc. per minute (0.7 per cent) in control dogs.

Comparison of Phenol-Talc Cardiopexy and Other Revascularization Procedures: Figure 2 illustrates the average extracoronary blood flow for the phenol-talc cardiopexy with partial coronary artery ligation as compared with other revascularization procedures performed with and without concomitant partial coronary artery ligation, as previously reported by our group. It may be seen that the only procedure studied which seemed to be as effective as the phenol-talc procedure without partial ligation was that of arterial implants and transplants to the myocardium. However, the technical aspects and the mortality rate were considerably greater with the latter procedure. Indeed, when partial coronary ligation was performed either preceding or immediately succeeding the major procedure of transplantation of carotid artery segments from the aorta to the myocardium, all eleven dogs succumbed either immediately or within 1 month postoperatively although no dogs died as a result of partial ligation alone.

It is our opinion that if the basically healthy canine heart, weakened only to the extent of the surgically-induced ischemia, was unable to tolerate a procedure of this magnitude, it is less likely that the already-damaged human heart could sustain such a procedure. In fact, Blalock and Sabiston[37] state that they have not performed internal mammary transplantation clinically despite some apparent beneficial effects of experimental carotid artery transplantation in dogs "because of a lack of conviction that it has greater merit than one of the simpler procedures."

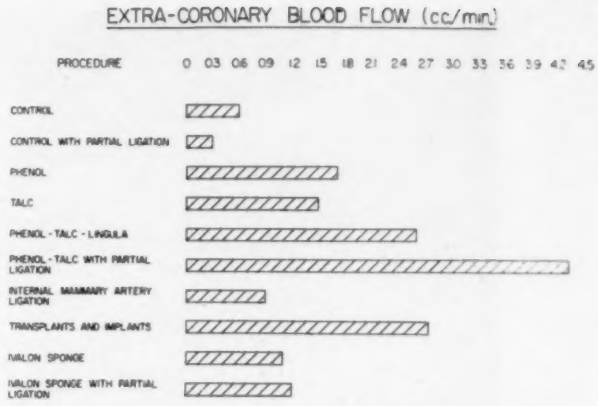
EXTRA-CORONARY BLOOD FLOW (cc/min.)
PROCEDURE
0 03 06 09 12 15 18 21 24 27 30 33 36 39 42 45
CONTROL
CONTROL WITH PARTIAL LIGATION
PHENOL
TALC
PHENOL - TALC - LINGULA
PHENOL - TALC WITH PARTIAL LIGATION
INTERNAL MAMMARY ARTERY LIGATION
TRANSPLANTS AND IMPLANTS
IVALON SPONGE
IVALON SPONGE WITH PARTIAL LIGATION

Fig. 2. The average extracoronary blood flow as determined for different revascularization procedures.

Results of experimental investigations of talc poudrage and phenol-talc cardiopexy have not been in agreement. Gage, Olsen and Chardack[38] studied talcum powder poudrage and the Beck 1 procedure in dogs. In order to produce coronary thrombosis aluminum wires were inserted into the coronary arteries either at cardiopexy or 1 month later. In comparison with control dogs, they found mortality rates and the incidence of gross myocardial infarcts to be essentially the same. They concluded that the procedures were not effective in promoting collateral circulation. Stone and Lord[39] have noted, however, that magnesium-aluminum wires placed in the dog's aorta produced thrombosis within 21 days. Indeed, Gage and coworkers[38] also reported that approximately half of their animals died suddenly 3 weeks after insertion of the thrombogenic wires; a maximum of 7 weeks elapsed after cardiopexy and before death. This period of time has been demonstrated[7] to be insufficient to permit effective revascularization to occur. Thus, Blalock and Sabiston[37] compared survival rates and infarct size following anterior coronary artery ligation in dogs 6 to 8 months after a procedure consisting of phenol de-epicardialization, talc poudrage and cardiopneumopexy. They found an 82 per cent survival rate and smaller infarct size in

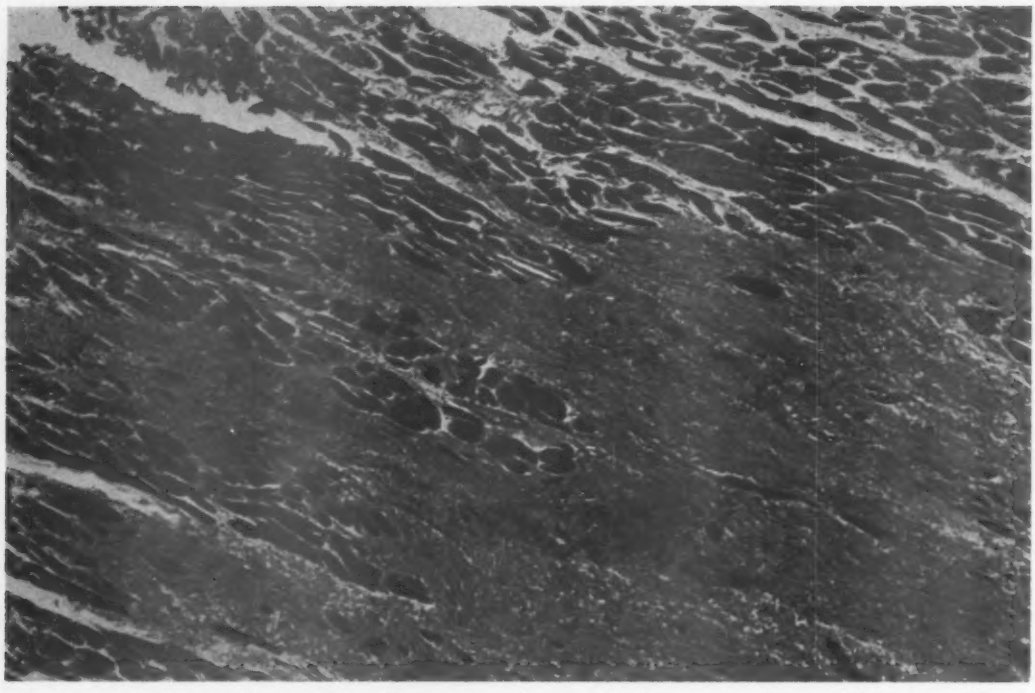

FIG. 3. Foci of dense hypocellular fibrous scar tissue replacing myocardium, with increased interstitial connective tissue separating the muscle fibers. (Hematoxylin and eosin stain; original magnification ×87.5.)

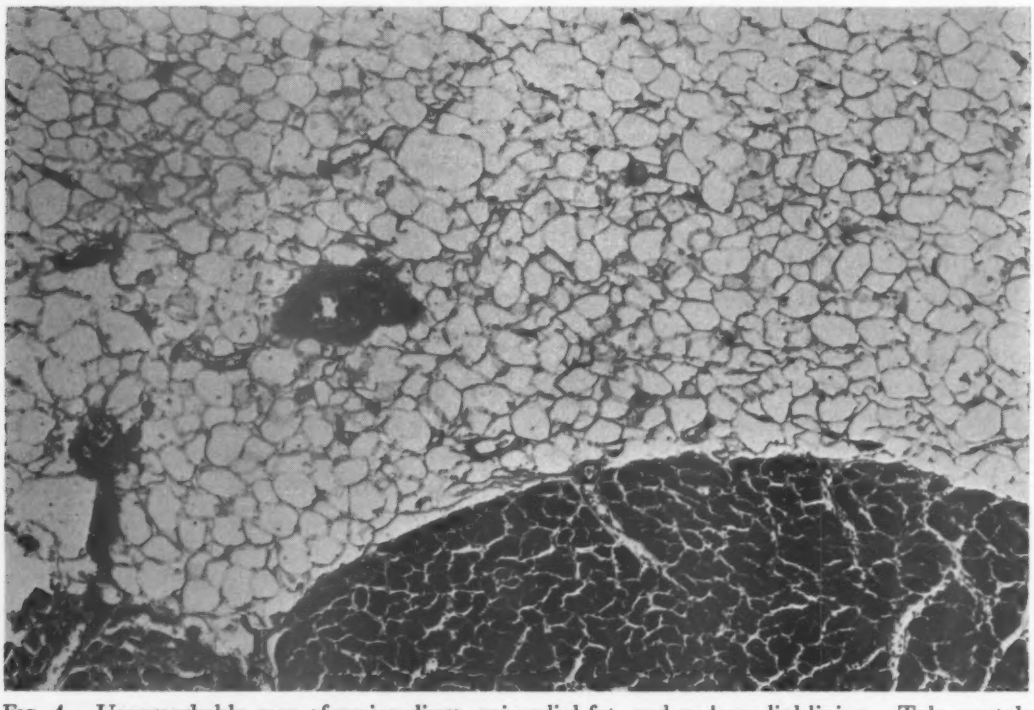

FIG. 4. Unremarkable area of pericardium, epicardial fat, and endocardial lining. Talc crystals were not found in such areas. (Hematoxylin and eosin stain; original magnification ×87.5.)

the experimental group than in the control group (30 per cent survival rate). Bakst and Loewe[40] performed talc poudrage in dogs and 3 months later measured retrograde blood flows from peripheral segments of the ligated circumflex coronary artery. They reported a threefold increase in blood flow over the expected normal value. For the reasons already indicated, however, we believe that the effectiveness of revascularization procedures in pro-

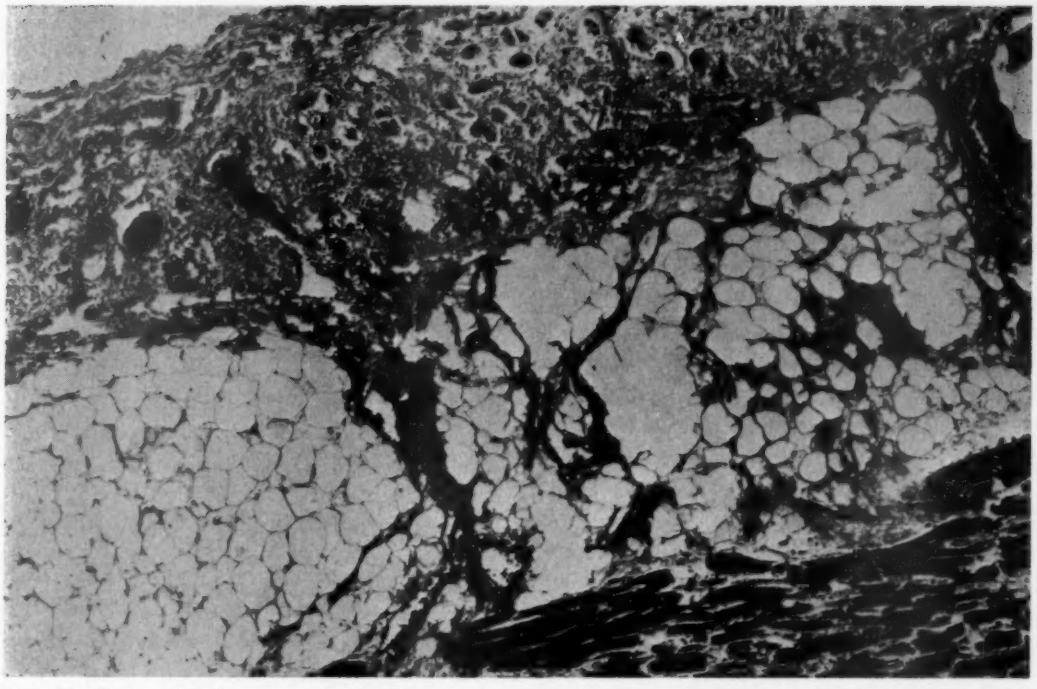

FIG. 5. Epicardial fat covered by a layer of granulation tissue composed of many foreign body giant cells. Thin walled blood vessels can be seen traversing the epicardial fat and entering the myocardium. Talc crystals were always found in such regions. (Hematoxylin and eosin stain; original magnification ×87.5.)

moting extracoronary collateralization may be more readily evaluated by measuring directly the amount of blood perfusing the heart.

ILLUSTRATIVE CLINICAL CASE REPORTS

Plachta, Thompson and Speer[41] have demonstrated pathologically the excellent vascularity of the granulation tissue resulting from talc poudrage. We have noted similar changes at postmortem examination in a patient treated by one of us.

CASE 1. A 71 year old widowed female physician was hospitalized on March 31, 1958 because of a suspected myocardial infarction following daily anginal attacks. The patient was a mild diabetic and had an 8 year history of angina pectoris for which she took vasodilators and narcotics liberally. In 1957 and 1958 she had myocardial infarcts and was maintained on continuous anticoagulant therapy. Her angina became increasingly severe, even at rest. Serial electrocardiograms on admission did not sustain the diagnosis of an acute myocardial infarction. Because of the severe angina at rest and the patient's strong desire for surgical relief, a talc poudrage was performed on April 22, 1958. The procedure consisted of the removal of a 5 cm. segment of costal cartilage; a 3 cm. pericardiotomy was performed and 2.75 gm. sterile talc U.S.P. was dispersed in the pericardial sac. Both internal mammary arteries were ligated incidentally. She was discharged on June 5, 1958. It was impossible to make a precise postoperative evaluation because of the patient's continued intake of narcotics. It is believed, however, that she required less vasodilators and the patient stated that she had milder and fewer anginal attacks. Fifteen months postoperatively the patient died. It was thought clinically that the patient died from other than cardiac causes.

An autopsy restricted to the heart was performed. The postmortem examination did not demonstrate adequate coronary atherosclerosis to account for the angina; rather, an unsuspected aortic stenosis was found. On gross examination, there was marked fibrous adherence of the epicardium and pericardium with obliteration of the pericardial sac. The heart, including attached pericardium, weighed 650 gm. Gross scarring of the myocardium was evident. The coronary arteries were patent throughout and had moderate atheromatous changes. The aortic valve measured 7.5 cm. in circumference. The cusps were thickened and sclerotic, containing several small calcified vegetations.

Figures 3, 4 and 5 depict representative areas of histologic sections. Figure 3 demonstrates the myocardial fibrosis which was distributed throughout the heart. Figure 4 illustrates an area of pericardium and adjacent epimyocardium with the epicardial fat appearing rather unremarkable, much as would be seen in an untreated heart. Interestingly, talc crystals could not be found in these areas. It is our opinion that the small pericardiotomy incision limited extensive dispersal of the talc about the pericardium.

Figure 5, in contrast, depicts a well-vascularized area of granulation tissue with many thin-walled blood vessels traversing the epicardial fat and entering the myocardium. On dark-field examination, numerous doubly-refractile crystals could be seen lying free in the granulation tissue and in many of the foreign body giant cells.

Comment: Similar changes in hearts examined as long as 10 years following talc poudrage were demonstrated by Plachta et al.[41] They believe that the talc acts as a focus of continued irritation to the pericardium, thereby effecting continued vasodilatation, resulting in adhesions with rich collateral vascularization. Indeed, the contrast between Figure 4, an area lacking talc crystals, and Figure 5, would seem to bear out their contentions.

A clinical case, treated by us with a phenol-talc procedure and representative of this method of revascularization is here presented.

Case 2. A 60 year old single woman was admitted to the hospital on December 1, 1958, because of increasingly severe angina decubitus. She had a long history of hypertension with known systolic blood pressures of 150 mm. Hg at age 18. In 1944, following blood pressures of 300/120–150 mm. Hg, a Smithwick sympathectomy was performed. In 1952, at cholecystectomy, the blood pressure was 170/100. In the 5 years preceding the admission under discussion she had increasingly severe angina on exertion and at rest. In the 9 months prior to admission she had four "borderline" coronary occlusions. She was receiving vasodilators, codeine and meperidine daily without relief. Her admission blood pressure was 192/94. An x-ray film of the chest was interpreted as showing "left ventricular and aortic accentuation." The cardiothoracic ratio was within normal limits. An electrocardiogram revealed depressed S-T segments and inverted T waves in lead aVF and flat T waves in the lateral precordial leads.

On December 4, 1958 a phenol-talc cardiopexy was performed. The fifth costal cartilege was removed in its entirety as well as 5 cm. of the fifth rib, anteriorly. A 6 cm. pericardiotomy was performed. Phenol (95 per cent) was applied to the epicardium and pericardium and 12 gm. of sterile talc was widely dispersed throughout the pericardial sac. The patient did well postoperatively, although vasopressors were required for 72 hours. She complained intermittently of pain in the anterior chest wall with radiation down both arms. These pains were relieved frequently by injections of sterile water. She was discharged January 10, 1959.

Since her discharge, her cardiac status has been excellent. Because of abdominal pains she was hospitalized in December 1959; the diagnoses of hiatus hernia and duodenal ulcer were established and she maintained an ulcer regimen.

She was last seen December 6, 1960 (2 years postoperatively) at which time she felt well, although complaining of occasional abdominal pain which frequently would precipitate an anginal attack. She was able to move about freely, had no angina at rest and was able to relieve her occasional exertional angina with nitroglycerin alone. At this time her pulse was 80 and regular. Blood pressure was 180/95 and examination of the heart was within normal limits. The chest wound was well healed.

In summary, this represents a 2 year follow-up study in a patient treated by phenol-talc cardiopexy, who now has a stable electrocardiographic record, is no longer incapacitated and, on the contrary, is comfortable without fear of impending death, with a reduced intake of vasodilators and narcotics. We believe that she is representative of the good clinical results obtainable with the procedure in carefully selected patients.

Comments

The phenol-talc procedure for myocardial revascularization has been demonstrated to be an effective means of bringing new blood to the ischemic heart. Moreover, the value of the procedure in enhancing already existing or promoting new intercoronary communications has been well demonstrated by Beck[6] who believes that this may indeed be its greatest virtue. There is no doubt that both of these effects are of genuine benefit to the patient with an anoxic myocardium. The prevention of electrical instability by widespread anastomoses among the major tributaries and the addition of new blood to myocardial cells bordering on anoxia and death are both of great value.

However, one must place this means of indirect revascularization in a perspective based on current and continuing advancements in this field. Sones'[42] technic for coronary angiography has developed so far that patients with symptomatic coronary artery disease may be subjected to this diagnostic tool when clinically indicated, with little fear. Indeed, further refinements and increased experience with coronary angiography in general may soon open the way for the routine application of this examination to asymptomatic patients of the proper age group as well. This will delineate the population into those with normal hearts and those with various degrees of coronary atherosclerosis.

Szilagyi and co-workers[43] in their postmortem study of 190 hearts showed that clinically manifest coronary atherosclerosis was generalized and hearts of clinically symptomatic subjects

could have been operated for cure by a direct surgical approach in only 13 per cent of instances. Noteworthy also is the fact that only 40 per cent of asymptomatic patients having coronary artery disease were operable for cure based on various technical criteria.

With the proper utilization of already available diagnostic tools symptomatic patients may be classified into those without coronary artery disease and those whose symptoms are of noncardiac etiology, those having a localized segmental block and those with widespread diffuse coronary sclerosis. Some of the latter will, of course, have disease of such extent that no surgical treatment would be indicated; some of those with localized disease might well have other contraindications to direct surgical attack. Bailey[44] has pointed out some of these contraindications: old age, congestive heart failure, hypertension, diabetes and renal disease. For the remainder of the patients with localized segmental disease, direct surgical approach may well be highly desirable. Longmire and Cannon[45] and Bailey[44] have presented the results of coronary endarterectomy performed clinically. Crafoord[46] has reported a means of enlarging the coronary arterial lumen by placing autogenous vein grafts as "patches" on the opened coronary arteries. For the large group of patients, however, without isolated blocks but with diffuse stenotic disease, as well as those for whom the direct approach is contraindicated, the phenol-talc revascularization procedure would be of genuine value.

With still greater experience in the use of diagnostic technics, the benefits of these procedures might well be offered to asymptomatic patients in the not-too-distant future on a prophylactic basis, with, thereby, a markedly increased salvage rate.

Summary and Conclusions

The phenol-talc procedure for myocardial revascularization has been studied by measurement of the extracoronary blood flow in dogs. In the presence of a relative myocardial ischemia this procedure has been demonstrated to bring to the heart 4.3 cc. per minute of new blood as compared with 0.6 cc. per minute and 0.3 cc. per minute in control procedures. A comparison of these results with those for other vascularization procedures has been made. The importance of direct measurement of the coronary blood flow as the means of assessing revascularization procedures has been stressed.

The well-vascularized granulation tissue resulting from cardiopexy has been illustrated. A representative clinical case and a discussion of the relationship of phenol-talc cardiopexy to the procedures for direct surgical attack on the coronary vessels have been presented. We believe that when indicated, the phenol-talc cardiopexy represents a satisfactory means of replenishing the myocardial blood supply with a minimum of surgical risk.

References

1. Beck, C. S. and Tichy, V. L. The production of a collateral circulation to the heart. I. An experimental study. *Am. Heart J.*, 10: 849, 1935.
2. Beck, C. S. A new blood supply to the heart by operation (editorial). *Surg. Gynec. & Obst.*, 61: 407, 1935.
3. Thompson, S. A. Development of cardiopericardial adhesions following the use of talc. *Proc. Soc. Exper. Biol. and Med.*, 40: 260, 1939.
4. Thompson, S. A. and Raisbeck, M. J. Cardiopericardiopexy: the surgical treatment of coronary arterial disease by the establishment of adhesive pericarditis. *Ann. Int. Med.*, 16: 495, 1942.
5. Schildt, P. E., Stanton, E. and Beck, C. S. Communication between the coronary arteries produced by the application of inflammatory agents to the surface of the heart. *Ann. Surg.*, 118: 34, 1943.
6. Beck, C. S. and Leighninger, D. S. Operations for coronary artery disease. *J.A.M.A.*, 156: 1226, 1954.
7. Harken, D. E., Black, H., Dickson, J. F., III, and Wilson, H. E. De-epicardialization: a simple effective surgical treatment of angina pectoris. *Circulation*, 12: 955, 1955.
8. Vansant, J. H. and Muller, W. H., Jr. Surgical procedures to revascularize the heart. *Am. J. Surg.*, 100: 572, 1960.
9. Beck, C. S. and Leighninger, D. S. Scientific basis for the surgical treatment of coronary artery disease. *J.A.M.A.*, 159: 1264, 1955.
10. Thompson, S. A. The surgical treatment of coronary heart disease. *Am. Pract.*, 8: 406, 1957.
11. Vineberg, A. and Walker, J. Six months to six years' experience with coronary artery insufficiency treated by internal mammary implantation. *Am. Heart J.*, 54: 851, 1957.
12. Dimond, E. G., Kittle, C. F. and Crockett, J. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *Am. J. Cardiol.*, 5: 483, 1960.
13. Lord, J. W., Jr. Surgery for coronary artery disease (editorial). *Surg. Gynec. & Obst.*, 110: 746, 1960.
14. Lord, J. W., Jr., Coryllos, E., Lowenfels, A. B., Dysart, R., Neuman, C. G., and Hinton, J. W. Evaluation of operations for revascularization of the myocardium by the study of coronary blood flow using extracorporeal circulation. *Surgery*, 43: 202, 1958.
15. Bowles, L. T., Tepper, R., Coryllos, E., Lowenfels, A. B., Postel, A., Brancadoro, G., Gel-

MAN, S. and LORD, J. W., JR. An experimental evaluation of operations for revascularization of the heart. *J. Thoracic and Cardiovasc. Surg.*, 40: 375, 1960.

16. FRIEDMAN, I. H., LANDEW, M., BOWLES, L. T., LOWENFELS, A. B., GELMAN, S. and LORD, J. W., JR. The effects of the Ivalon sponge procedure on extra-coronary blood flow: an experimental evaluation. *Ann. Surg.* In press.
17. GOLDSMITH, E. I. and MAYER, H. J. Objective evaluation of myocardial blood supply in vivo through observation of acute changes in myocardial temperature. *Surg. Forum*, 11: 197, 1960.
18. SNYDER, D. D., SEVELIUS, G., JOHNSON, P. L., CAMPBELL, G. S. Coronary blood flow measured by a surface counting technique. *Surg. Gynec. & Obst.*, 3: 371, 1960.
19. ALLELA, A., WILLIAMS, F. L., BOLENE-WILLIAMS, C. and KATZ, L. N. Interrelation between cardiac oxygen consumption and coronary blood flow. *Am. J. Physiol.*, 183: 570, 1955.
20. ZOLL, P. M., WESSLER, S. and SCHLESINGER, M. J. Interarterial coronary anastomoses in the human heart with particular reference to anemia and relative cardiac anoxia. *Circulation*, 4: 797, 1951.
21. PEARL, F., JOSEPH, R. and CITRET, C. Implants of the internal mammary artery into ischemic dog ventricles. *Arch. Surg.*, 79: 497, 1959.
22. GREGG, D. E., THORNTON, J. J., and MAUTZ, F. B. The magnitude, adequacy and source of the collateral blood flow in chronically occluded coronary arteries. *Am. J. Physiol.*, 127: 161, 1939.
23. KLINE, J. L. Myocardial revascularization. II. Intra-myocardial vs. extra-myocardial source of collateral circulation. *Guy's Hosp. Rep.*, 108: 271, 1959.
24. LEIGHNINGER, D. S. A laboratory and clinical evaluation of operations for coronary artery disease. *J. Thoracic Surg.*, 30: 397, 1955.
25. BLUMGART, H. L. and ZOLL, P. M. Pathologic physiology of angina pectoris and acute myocardial infarction. *Circulation*, 22: 301, 1960.
26. ECKENHOFF, J. E., HAFKENSCHIEL, J. H. and LANDMESSER, C. M. The coronary circulation in the dog. *Am. J. Physiol.*, 148: 582, 1947.
27. LOWENFELS, A. B., NEUMANN, C. G., WADE, W. H., VON WEDEL, J., LORD, J. W., JR. and HINTON, J. W. The effects of gradual occlusion of the coronary arterial circulation in dogs and pigs. *Surg. Forum*, 7: 302, 1957.
28. SCHLESINGER, M. J. An injection plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.*, 15: 528, 1938.
29. PRINZMETAL, M., SIMKIN, B., BERGMAN, H. C. and KRUGER, H. E. Studies on the coronary circulation. II. *Am. Heart J.*, 33: 420, 1947.
30. GAGE, A. A., OLSON, K. C. and CHARDACK, W. M. Experimental coronary thrombosis in the dog. *Ann. Surg.*, 143: 535, 1956.
31. BERMAN, J. K., FIELDS, D. C. JUDY, J., MARI, U. and PARKER, R. J. Gradual vascular occlusion. *Surgery*, 39: 399, 1956.
32. LITVAK, J., SIDERIDES, L. E. and VINEBERG, A. M. The experimental production of coronary artery insufficiency and occlusion. *Am. Heart J.*, 53: 505, 1957.
33. LOWENFELS, A. B., WADE, W. H., NEUMAN, C. G. and LORD, J. W., JR. Experimental study of a gradually closing delayed-action blood vessel clamp. *Arch. Surg.*, 74: 574, 1957.
34. PIANETTO, M. B. The coronary arteries of the dog. *Am. Heart J.*, 18: 403, 1939.
35. KLINE, J. L. Myocardial revascularization. I. The fallacy of the anterior coronary challenge. *Guy's Hosp. Rep.*, 108: 262, 1959.
36. WIGGERS, C. J. The problem of functional coronary collaterals. *Exper. Med. & Surg.*, 8: 402, 1950.
37. BLALOCK, A. and SABISTON, D. C., JR. The coronary artery disease problem. *West. J. Surg.*, 67: 18, 1959.
38. GAGE, A. A. OLSON, K. C. and CHARDACK, W. M. Cardiopericardiopexy—an experimental evaluation. *Ann. Surg.*, 147: 289, 1958.
39. STONE, P. and LORD, J. W., JR. An experimental study of the thrombogenic properties of magnesium and magnesium-aluminum wire in the dog's aorta. *Surgery*, 30: 987, 1951.
40. BAKST, A. A. and LOEWE, L. The surgical therapy of occlusive coronary artery disease. *Am. J. Cardiol.*, 1: 340, 1958.
41. PLACHTA, A., THOMPSON, S. A. and SPEER, F. D. Pericardial and myocardial vascularization following cardiopericardiopexy. *Arch. Path.*, 59: 151, 1955.
42. SONES, F. M., JR., SHIREY, E. K., PROUDFIT, W. L. and WESTCOTT, R. N. Cine-coronary arteriography. Proceedings of the 32nd Scientific Sessions, American Heart Association, Philadelphia. Abst. in: *Circulation*, 20: 773, 1959.
43. SZILAGYI, D. E., MCDONALD, R. T. and FRANCE, L. C. The applicability of angioplastic procedures in coronary atherosclerosis. *Ann. Surg.*, 148: 447, 1958.
44. BAILEY, C. P., MORSE, D. P. and LEMMON, W. M. Thromboendarterectomy for coronary artery disease. *Am. J. Cardiol.*, 5: 3, 1960.
45. LONGMIRE, W. P., JR., CANNON, J. A. and KATTUS, A. A. Direct vision coronary endarterectomy for angina pectoris. *New England J. Med.*, 259: 993, 1958.
46. CRAFOORD, C. Some aspects of surgery for coronary disease. *Surgery*, 49: 215, 1961.

New Method

Localization of Right to Left Shunts with an Intravascular Polarographic Anode Sensitive to Ascorbic Acid*

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THE DETECTION and localization of right to left intracardiac and extracardiac shunts may be accomplished by selective angiography,[1,2] dye indicator dilution technics,[3–5] and indicator dilution procedures using radioactive substances.[6–8] Electrode sensors have been used to detect saline[9] and hydrogen-saturated saline[10] indicators. The purpose of this communication is to report the development of intravascular polarographic electrodes which are sensitive to ascorbic acid and to demonstrate their value in the localization of right to left shunts.

THEORY

Polarographic *cathodes* have been widely used in biology to measure oxygen. The less known polarographic *anodes* are depolarized, and hence allow current to flow, by certain readily oxidizable substances such as ascorbic acid. Anodically polarized platinum electrodes are not sensitive to oxygen.

The Clark electrode[11] utilizes an applied voltage of −0.6 volt for the electroreduction of oxygen. Polarograms, or current voltage diagrams of electrodes in ascorbic acid solutions, indicate that the electro-oxidation plateau for ascorbate is about +0.85 volt. Both platinum cathode and platinum anode may be used with a silver reference electrode. Oxidation of ascorbic acid to dehydroascorbic acid with the release of two electrons occurs in the presence of the anode.

MATERIALS AND METHODS

The Anode: Platinum beads with a glass-insulated shank were sealed into polyethylene tubing which was used as a catheter. Alternately, 22 or 28 gauge platinum wire, insulated with the epoxy resin enamel G, was used for introduction into small peripheral arteries. The insulation was removed from the wire so as to leave an exposed tip of 1 to 3 mm., and the cut end was beveled.

The Cathode: An "L" shaped piece of sheet silver, or a heavily plated electrocardiogram electrode, was used as the cathode or reference electrode. Conventional electrocardiographic paste was used to make contact with the skin.

The Circuit: The polarizing circuit shown in Figure 1 was devised so that voltages could be adjusted up to 1.4 volts. The current from the anode can be reduced in half or in fourth by the sensitivity switch shown. The output terminals, labeled "galvanometer," can be connected to recording potentiometers.

Animal Experiments: The platinum anode was introduced into the arch of the aorta through the femoral or carotid artery in such a way that the active surface of the tip was in a free-flowing arterial stream. Ascorbate solutions were injected into the vena cava of anesthetized dogs, near the right atrium, through a polyethylene catheter. Introduction of the tip into a branch of the aorta was the most common cause of a sluggish response of the electrode.

Human Studies: A platinum wire electrode was inserted for a distance of about 0.5 cm. into the exposed common femoral artery at the groin or the brachial artery at the antecubital fossa of patients under-

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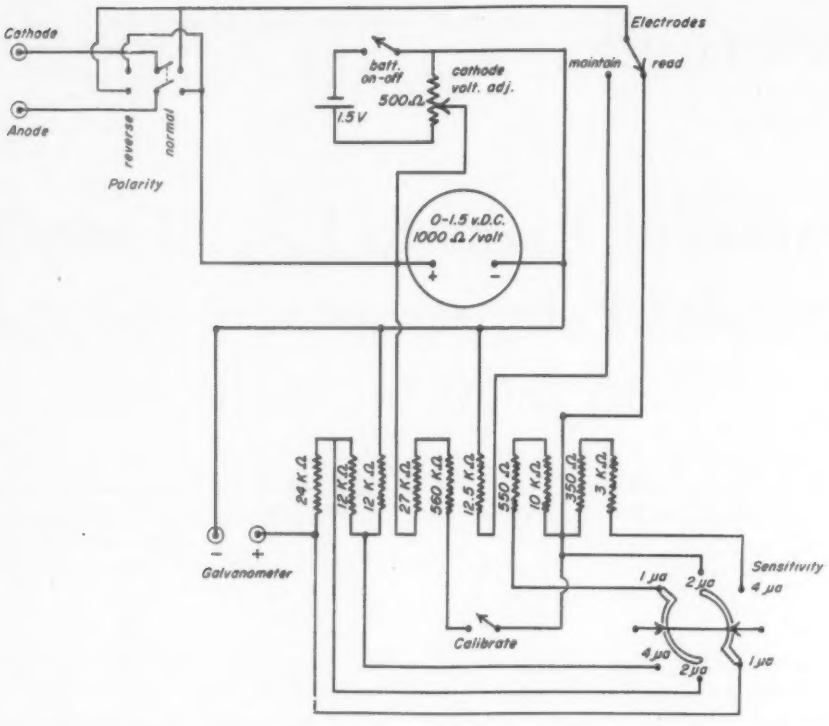


FIG. 1. Biopolarographic circuit for use with galvanometer or 10 mv. potentiometer.

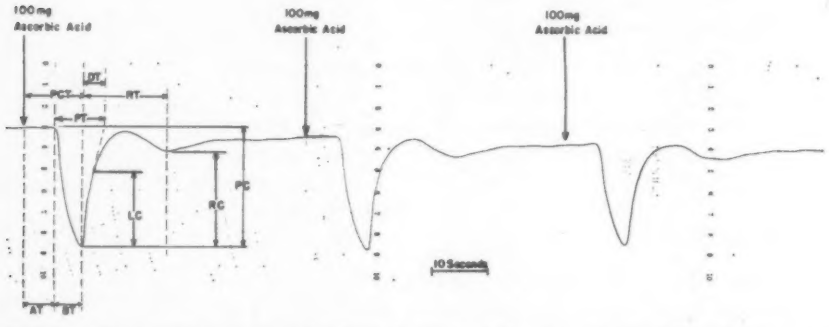
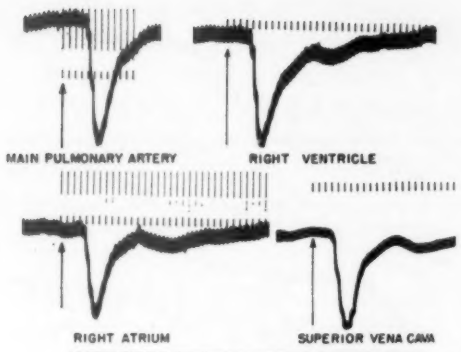


FIG. 2. Consecutive curves obtained from the injection of ascorbic acid into the superior vena cava of an anesthetized dog. The anode was an insulated 28 gauge platinum wire. Records were obtained with a photoelectric galvanometer. In this tracing 10 cm. = 3.84 μa. The applied voltage was 0.8 volt. AT = appearance time; BT = build-up time; PCT = peak concentration time; RT = recirculation time; PT = passage time; DT = disappearance time; PC = peak concentration; RC = maximal recirculation concentration; LC = least concentration.

going routine cardiac catheterization for the diagnosis of congenital heart disease. Some studies were done with the anode mounted in a polyethylene catheter which was advanced into the aorta from the brachial artery. Ascorbic acid was injected at various sites in the lesser circulation through a cardiac catheter.

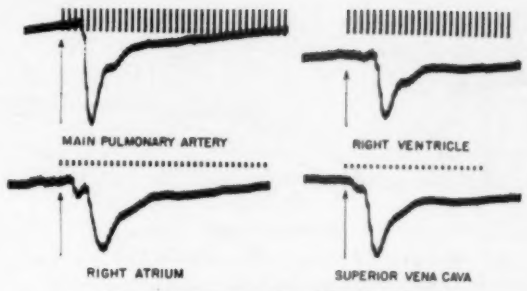
Dosage of Ascorbic Acid: Isotonic sodium chloride was used to dilute sterile sodium ascorbate preparations. With high sensitivity instruments as little as 10 mg. can be used for each injection, but multiple doses as high as 25 to 100 mg. of ascorbate can be administered safely. The volume of solution did not exceed 2 ml. A greater current is produced from a larger electrode.

Method of Right Heart Catheterization: The patients were catheterized through the saphenous vein at the groin or the right medial antecubital vein while under light sedation with a mixture of meperidine, chlorpromazine and promethazine.[12] An image intensifier (Phillips) and a closed circuit television camera and screen were used to monitor the position of the catheters. Statham strain gauges and oscillographic cameras (Electronics for Medicine) were used to measure pressures. Oxygen saturation of blood samples was



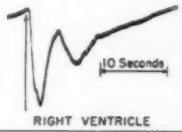
	PRESSURE mm Hg	BLOOD O_2 SAT. (%)
BRACHIAL ARTERY	95/60	93
PULMONARY ARTERY	28/10	75
RIGHT VENTRICLE	25/0	78
RIGHT ATRIUM	5	74
SUPERIOR VENA CAVA	–	72
INFERIOR VENA CAVA	–	76

FIG. 3. *Normal dynamics in right side of the heart.* Curves obtained after the injection of 10 mg. ascorbic acid at various sites in the lesser circulation. Platinum wire anode in brachial artery. Arrows indicate instant of injection. Time lines = 1 second. Records obtained with a d.c. amplifier.



	PRESSURE mm Hg	BLOOD O_2 SAT.(%)
AORTA	113/72	95
PULMONARY ARTERY	115/53	79
RIGHT VENTRICLE	115/0	81
RIGHT ATRIUM	2	71
SUPERIOR VENA CAVA	–	72
INFERIOR VENA CAVA	–	72

FIG. 4. *Ventricular septal defect.* Records obtained after injection of 10 mg. ascorbic acid at various sites in the lesser circulation. Platinum wire anode in femoral artery. Arrows indicate instant of injection. Time lines = 1 second. Records obtained with a d.c. amplifier. Although the oxygen saturation was normal, the ascorbic acid curves indicate a right to left shunt.



	PRESSURE mm Hg	BLOOD O_2 SAT. (%)
FEMORAL ARTERY	105/80	78
PULMONARY ARTERY	10/0	62
RIGHT VENTRICLE INFUNDIBULUM BODY	 36/0 103/0	 56 55
RIGHT ATRIUM	0	60
SUPERIOR VENA CAVA	–	61
INFERIOR VENA CAVA	–	61

FIG. 5. *Tetralogy of Fallot.* Injection of 10 mg. ascorbic acid into right ventricle with platinum wire anode in femoral artery. Arrow indicates instant of injection. Record obtained with a d.c. amplifier. The early appearance time identifies the right to left shunt.

measured spectrophotometrically by a modification of the procedure of Gordy and Drabkin.[13]

RESULTS

Animal Experiments: One hundred and forty injections of ascorbate were made in sixteen dogs. Figure 2 shows a galvanometer tracing obtained from three successive injections of 100 mg. of sodium ascorbate.

Reproducible currents were obtained following the injection of identical doses of ascorbic acid. Expressed in microamperes, the peak concentration varied between 1.8 and 2, maximal recirculation concentration from 1.5 to 1.7 and the least concentration from 1.1 to 1.2. The time components varied from animal to animal, as would be expected. Correcting for the base line increase, which represents an increasing blood level of sodium ascorbate, the area under the curves shown in Figure 2 was between 1.12 and 1.21 square inches.

Human Studies: Representative curves ob-

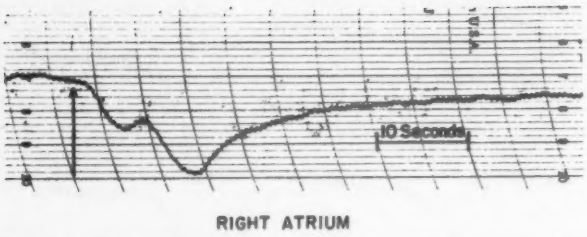


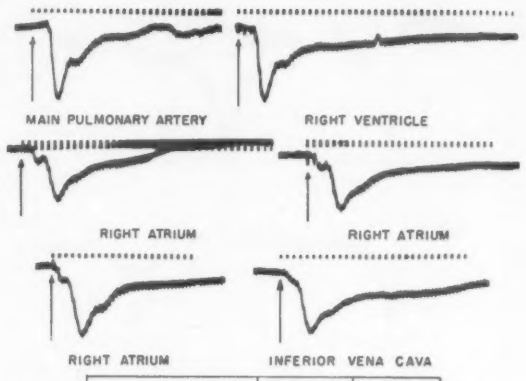
FIG. 6. *Tetralogy of Fallot.* Injection of 50 mg. ascorbic acid into right atrium. Arrow indicates instant of injection. Anode was a platinum bead insulated in glass and mounted in a polyethylene catheter which was advanced into the ascending aorta. Records obtained with a photoelectric galvanometer. (5 cm. = 1.92 μa.) The early appearance time identifies the right to left shunt.

tained from the catheterization of twenty patients are shown in Figures 3 to 7. Figure 3 indicates the curves obtained from a 7 year old girl with mild congenital *aortic stenosis*. Although the arterial oxygen saturation is at the lower limit of normal for this laboratory a right to left shunt was excluded by the curves. Appearance times were identical.

Figure 4 summarizes the data obtained from the catheterization of an 8 year old boy with a *ventricular septal defect* through which the catheter tip could be guided into the aorta. Calculated pulmonary arterial resistance was 1,184 dynes second cm.$^{-5}$, but the normal arterial saturation suggested the absence of a right to left shunt. However, since abnormal, double peak curves were obtained after injection of ascorbate into the superior vena cava, the right atrium, and the right ventricle, but not the pulmonary artery, a right to left shunt was demonstrated. The near-normal curve shown for the ventricular injection may be due to the fact that the injection was made selectively away from the defect.

The depolarization current obtained from a platinum anode in the femoral artery, following the injection of 10 mg. of ascorbic acid into the right ventricle of a 7 year old girl having *tetralogy of Fallot*, is shown in Figure 5. The large early peak, together with an appearance time of less than 1 second, illustrates the large right to left shunt. Somewhat smaller early peaks were recorded following injections into the right atrium and vena cava, indicating that in this case the ascorbate may have been injected toward the defect when the catheter tip was in the right ventricle.

Figure 6 is a galvanometer tracing of the anode current following injection of ascorbate into the right atrium of a 21 year old man with *tetralogy of Fallot*. This patient had undergone a left-



	PRESSURE mm. Hg	BLOOD O_2 SAT. (%)
FEMORAL ARTERY	134/84	91
PULMONARY ARTERY	122/60	81
RIGHT VENTRICLE	140/3	72
RIGHT ATRIUM	6/-3	68
SUPERIOR VENA CAVA	–	67
INFERIOR VENA CAVA	–	73

FIG. 7. *Patent ductus arteriosus.* Injection of 10 mg. ascorbic acid at various sites in the lesser circulation. Platinum wire anode in femoral artery. Arrows indicate instant of injection. Time lines = 1 second. Records obtained with d.c. amplifier. The early appearance time after injection into right atrium and inferior vena cava localizes the atrial septum as the site of the right to left shunt.

sided Blalock-Taussig operation at the age of 13. Similar curves were obtained from the vena cava and the right ventricle, but a normal curve, with an appearance time of 7 seconds, was obtained from the pulmonary artery. The small regular fluctuations easily seen on this curve are due to pulsations in blood flow which decrease the diffusion layer in the immediate proximity of the anode surface. Such pulsations serve to indicate that the electrode is in a free-flowing blood stream.

The localization of a small right to left shunt at a site other than the major defect is illustrated in Figure 7. This 6 year old boy had *patent ductus arteriosus*, marked pulmonary hypertension (1,200 dynes second cm.$^{-5}$) and, as found by the ascorbate injections, an *atrial septal defect*. The low femoral arterial saturation by itself could be explained by depressed respiration induced by the sedation, or by a right to left shunt. The 3-second appearance time following injections downstream from the atrium was reduced to 0.5 to 1.5 seconds following injections into the right atrium or the vena cava. The small early peak indicates that the shunt is very small and may be due to a patent foramen ovale.

COMMENTS

For the localization of right to left shunts the arterial polarographic anode technic is useful

because it obviates the need for blood sampling. This is particularly advantageous in infants in whom significant volumes of blood may be needed for inscription of dye dilution curves and in whom the curves are attenuated in traversing the fine cannulas necessary. The indicator substance is innocuous, and because the electrode is insensitive to oxygen, it has a low base line current and returns to this base line rapidly following injections of ascorbate. Although a direct comparison with other dilution technics has not been made, it is clear that small right to left shunts can be detected and localized.

The polarizing voltage can be obtained from a small battery and the circuit can be readily adapted to conventional amplifiers and recording equipment.

Polarographic measurements can be quantitative in terms of current and ascorbate concentration, and work is in progress toward this end. It appears possible to design a platinum electrode catheter, or arterial needle electrode, which could serve as both a hydrogen electrode[14, 15] or as a polarographic electrode.

Summary

The development of an intravascular polarographic anode which detects ascorbic acid is reported and its value in detecting and localizing right to left shunts is demonstrated.

References

1. Chavez, I., Dorbecker, N. and Celis, A. Direct intracardiac angiocardiography: its diagnostic value. *Am. Heart J.*, 33: 560, 1947.
2. Jonsson, G. Selective visualization in angiocardiography. *J. Fac. Radiologists*, 3: 125, 1951.
3. Hamilton, W. F., Moore, J. W., Kinsman, J. M. and Spurling, R. G. Studies on circulation: further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions. *Am. J. Physiol.*, 99: 534, 1932.
4. Hetzel, P. S., Swan, H. J. C. and Wood, E. H. The application of indicator dilution curves in cardiac catheterization. In: Zimmerman, H. A. Intravascular Catheterization, p. 539. Springfield, Ill., 1959. Charles C Thomas.
5. Swan, H. J. C. Indicator dilution methods in the diagnosis of congenital heart disease. *Prog. Cardiovasc. Dis.*, 2: 143, 1959.
6. Nylin, G. and Celander, H. Determination of blood volume in the heart and lungs and the cardiac output through injection of radiophosphorus. *Circulation*, 1: 76, 1950.
7. Pritchard, W. H., MacIntyre, W. J., Schmidt, W. C., Brofman, B. L. and Moore, D. J. The determination of cardiac output by continuous recording system utilizing iodinated (I^{131}) human serum albumin. II. Clinical studies. *Circulation*, 6: 572, 1952.
8. Case, R. B., Hurley, H. W. and Keating, P. Detection and measurement of circulatory shunts by use of a radioactive gas. *Prog. Cardiovasc. Disc.*, 2: 186, 1959.
9. Booth, R. W., Ryan, J. M. and Goodwin, R. S. A saline conductivity method for detection of cardiac shunts by indicator-dilution technique. *Circulation Res.*, 6: 142, 1958.
10. Clark, L. C., Bargeron, L. M., Lyons, C., Bradley, M. H. and McArthur, K. T. The detection of right to left shunts with an arterial potentiometric electrode. *Circulation*, 22: 949, 1960.
11. Clark, L. C. Monitor and control of blood and tissue oxygen tensions. *Tr. Am. Soc. Artificial Internal Organs*, 2: 41, 1956.
12. Smith, C., Rowe, R. D. and Vlad, P. Sedation of children for cardiac catheterization with an ataractic mixture. *Canad. Anaest. Soc. J.*, 5: 35, 1958.
13. Gordy, E. and Drabkin, D. L. Spectrophotometric studies. XVI. Determination of the oxygen saturation of blood by a simplified technique applicable to standard equipment. *J. Biol. Chem.*, 227: 285, 1957.
14. Clark, L. C. and Bargeron, L. M. Left to right shunt detection by an intravascular electrode with hydrogen as an indicator. *Science*, 130: 709, 1959.
15. Clark, L. C. and Bargeron, L. M. The detection and direct recording of left to right shunts with the hydrogen electrode catheter. *Surgery*, 46: 797, 1959.

Case Reports

Complete Interruption of the Aorta*

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Guadalajara, Mexico

A recent review of the literature on complete interruption of the aorta at the level of the isthmus revealed only forty reported cases.[1–5,7–9] The majority of these patients had a limited lifespan; only the one studied by Donzelot et al.[6] reached the age of 11 years (Table 1).

The case of a patient studied recently in the Hospital Civil of Guadalajara, Mexico, is of interest because there were some unusual clinical features and the patient reached the age of 14 years. The principal malformation was corrected successfuly by surgery.

Case Report

This 14 year old boy was the product of an uncomplicated, full term delivery. However, the mother had had hyperemesis and frequent respiratory infections during the first trimester. One sibling (the previous child) was cyanotic and died a few hours after birth.

The patient has had frequent and severe infections of the lower respiratory tract, beginning with severe bronchopneumonia during the first months of life. Dyspnea, hemoptysis and profuse epistaxis have become prominent during recent infectious episodes.

The patient has always had limited physical endurance, but it was not until he was 5 years old during one of the respiratory infections, that a heart murmur was discovered. At the age of 8 the patient complained of frequent frontooccipital headaches and at the age 13 years occasional fainting spells developed. At the age of 14 years the patient had a severe infectious condition, thought to be subacute bacterial endocarditis. This was not proved. Despite negative blood cultures 20 million units of penicillin was given daily for a 2 week period, the patient responded well.

Physical examination revealed an underdeveloped boy who appeared younger than the stated age of 14 years. The carotid pulsations were regular and had a bounding quality. A moderately harsh systolic murmur accompanied by a thrill was present over the neck vessels. The pulse in these vessels and in the suprasternal and supraclavicular areas was bounding in type. The chest was asymmetrical due to a large bulge in the precordial region. A well-developed collateral circulation was both visible and palpable over the posterior aspect of the chest. A diffuse precordial heave was present, the greatest impulse being in the epigastrium. There was a systolic thrill palpable in the epigastrium and along the left sternal border, particularly in the fifth and sixth intercostal spaces. The apical impulse was diffuse and easily palpable in the seventh left intercostal space. Percussion revealed (in addition to cardiomegaly) an area of dullness extending 3 cm. to the left of the sternum in the second and third intercostal spaces. A systolic thrill was palpable in the same area. The heart rate was 90 per minute and the rhythm was regular. A harsh systolic murmur was heard along the left sternal border with grade 4 intensity in the fifth and sixth left intercostal spaces. This murmur extended toward the left axilla and the back. A soft, grade 1 to 2 systolic murmur was heard at the apex. The second heart sound was accentuated in the second and third intercostal spaces on both sides of the sternum. The blood pressure was 220/120 mm. Hg in both arms and 120/80 mm. Hg in the legs. There was slight cyanosis of the toes, increasing with physical exertion. Examination of the eye grounds disclosed moderate vascular arteriolar sclerosis. The hemoglobin and red blood cell counts were within normal limits.

The roentgenogram of the chest in the posteroanterior view (Fig. 1A) revealed moderate cardiomegaly. Both ventricles were enlarged. The pulmonary artery

* From the Hospital Civil, Guadalajara, Mexico.

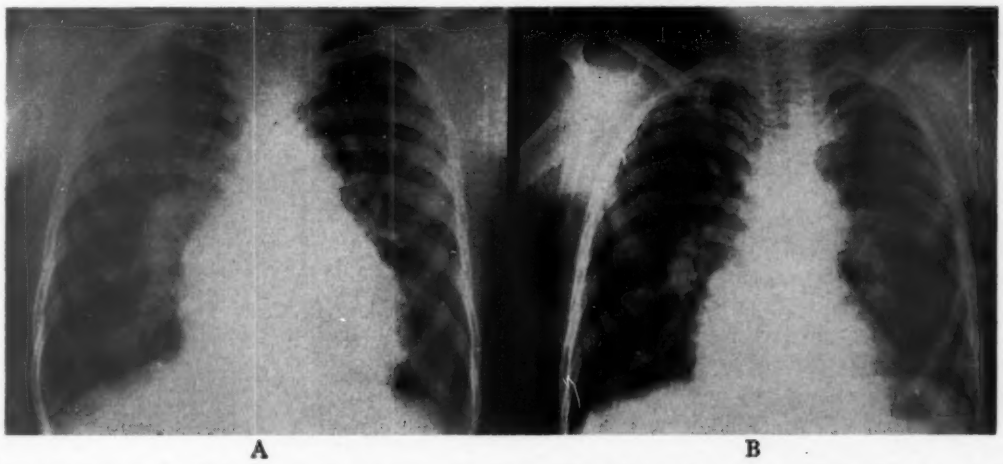
TABLE 1
Summary of Twenty-Seven Reported Cases of Complete Interruption of the Aorta

Author	Year of Publication	Age and Sex	Deceased	Underwent Operation
Seidel[23]	1818	Hours, M	Yes	No
Letterer[18]	1923	5 days, F	Yes	No
Abbott[2]	1927	15 days, ...	Yes	No
Abbott[2]	1927	1 day, ...	Yes	No
Abbott[2]	1927	6 mo., ...	Yes	No
Gaspar[13]	1929	6 mo., F	Yes	No
Evans[8]	1933	5 days, M	Yes	No
Evans[8]	1933	2 days, F	Yes	No
Evans[8]	1933	11 days, M	Yes	No
Hamburger[14]	1937	1 mo., M	Yes	No
Wiseman et al.[27]	1948	71 hours, M	Yes	No
Taussig[26]	1960	...	Yes	No
Stewart[24]	1948	45 hours, F	Yes	No
Jew et al.[15]	1952	53 hours, M	Yes	No
Kintner[16]	1953	14 hours, M	Yes	No
Donzelot[6]	1954	11 yr., ...	Yes	No
Barger et al.[4]	1954	9 days F	Yes	No
Dorney et al.[7]	1955	5 yr., F	Yes	No
Merril et al.[19]	1957	3 yr., F	?	Yes
Everts-Suárez et al.[11]	1959	3 days, M	Yes	No
Espino-Vela et al.[9]	1959	3 yr., F	Yes	No
Abrams[3]	1958	4 yr., ...	Yes	No
Fournier et al.[12]	1960	2 mo., F	Yes	No
Noonan et al. (4 cases)[20]	1958	20 days, ...	Yes	No
Noonan et al.[21]	1958	3 mo., ...	Yes	No
Quie et al.[22]	1959	...	Yes	Yes
Ruiz Villalobos et al.	1961	14 yr., M	No	Yes

was prominent; the hilar vascular shadows were increased and there were a few notchings at the lower margin of some ribs.

The electrocardiogram (Fig. 2) revealed an unusual axis deviation with deep S waves in leads I, II, III and aVF, and prominent R in aVR. There were Rsr's' complexes in lead V_1 and diphasic deflections (RS) in V_2 to V_4. The morphology of the ventricular complexes in leads I, V_5 and V_6 was qRS, with positive peaked T waves. The T waves were inverted in V_1 to V_3. The tracing was interpreted as suggestive of incomplete right bundle branch block, biventricular hypertrophy, left ventricular diastolic overloading and right ventricular diastolic and systolic overloading.

Cardiac Catheterization: These data led to the clinical



A B

FIG. 1. Roentgenograms in P-A view. A, preoperative film. Note the enlargement of the heart and the profuse vascularity of the lungs. B, postoperative film. Note the smaller heart size and the diminished vascularity of the lungs.

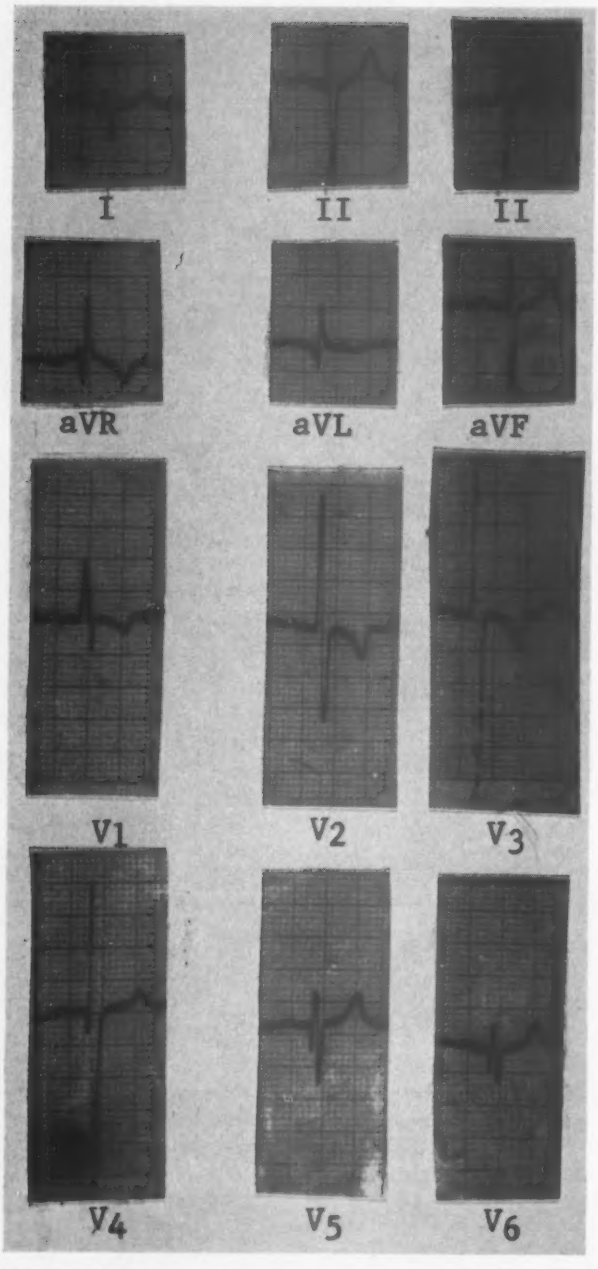


FIG. 2. Electrocardiogram suggestive of partial right bundle branch block and biventricular hypertrophy.

diagnosis of coarctation of the aorta, patent ductus arteriosus and ventricular septal defect. Cardiac catheterization[28] disclosed the presence of a patent ductus arteriosus which was traversed by the catheter (Fig. 3). Data from this study are shown in Table II.

The patient was referred for surgery with the diagnosis of patent ductus arteriosus and coarctation of the aorta. Ventricular septal defect was not entirely excluded as an additional possibility.

Surgical Findings: The heart was considerably enlarged. A thrill was felt over its entire surface. The intercostal arteries, especially the first two or three

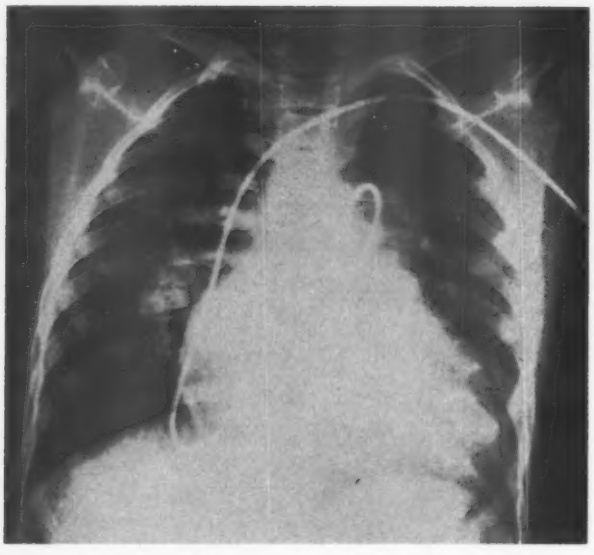


FIG. 3. A catheter is shown within the heart and in the aorta, through a "patent ductus arteriosus"; actually it is entering the initial portion of the descending aorta which arose from the pulmonary artery.

pairs were dilated and tortuous. The aorta arose from the left ventricle in a normal fashion, ascended normally and gave origin to the right innominate artery, the left carotid artery and the left subclavian artery. These vessels were normally distributed. The pulmonary artery was approximately three times normal size and larger than the aorta. It arose in the usual fashion from the right ventricle. The right pulmonary artery was not remarkable, the left pulmonary artery arose at a sharp angle and was extremely dilated. The descending aorta emerged from this branch at the site where the ductus arteriosus is usually found, when patent. The first portion of this descending aorta was narrow in comparison to the remainder of the

TABLE II
Catheterization Findings

Site	Oxygen Content (vol. %)	Oxygen Saturation (%)	Blood Pressure (mm. Hg)
Superior vena cava	12.87	74.73	...
Right atrium	12.75	74.04	(7)*
Right ventricle	12.87	74.73	90/1.6 (38)
Pulmonary artery	12.87	74.73	90/36.3
Right			(51)
Left	12.75	74.04	...
Aorta	12.99	75.43	117/74 (88)
Femoral artery	13.04	75.60	...
Brachial artery	14.89	86.48	...
Pulmonary capillary	...	...	(18)

* Numbers in parentheses indicate mean pressures.

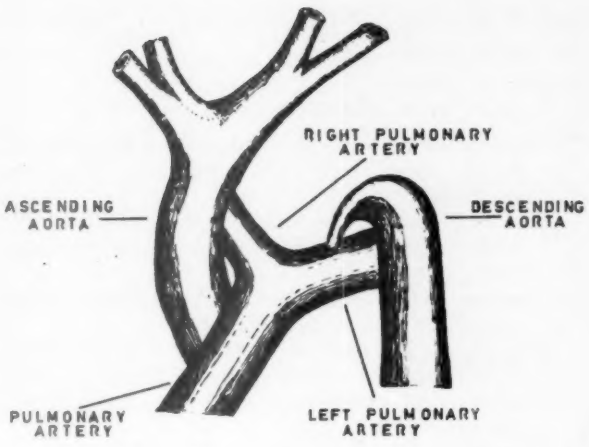
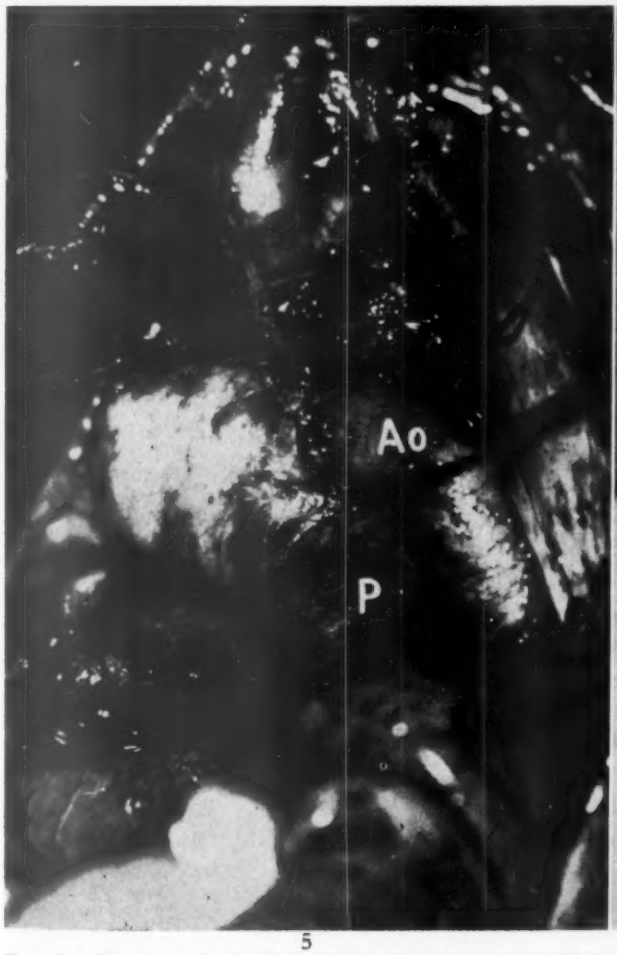


FIG. 4. Drawing showing the aorta and its branches before the operation.

vessel. In fact, this first part was actually the patent ductus arteriosus connecting the two vessels without a definite line of demarcation. These relationships are diagrammed in Figure 4. The distribution of the vagus and the recurrent laryngeal nerves was that usually seen in cases of patent ductus arteriosus. Figure 5 shows the aorta arising from the left pulmonary artery, pulled back slightly with a tape.

After the anatomy of the vessels was understood clearly, the descending aorta was clamped for 15 minutes and intravascular pressure readings were obtained by a needle inserted into the pulmonary artery. Because there was no significant alteration in pressure, the aorta was severed from the pulmonary artery. A Teflon graft, 15 cm. long and 2 cm. in diameter, was anastomosed end to side with the left subclavian artery; the lower end of the graft was anastomosed end to end with the distal portion of the descending aorta. Figure 6 shows the portion of this graft, which functioned perfectly. Pressures and blood samples were obtained in the aorta, in the graft and in the pulmonary artery at the end of the procedure. Oxygen saturation was identical in the graft and in the aorta and equal to 89.07 per cent. Both had equal pressures of 135/80 mm. Hg. Oxygen saturation in the pulmonary artery was 75.5 per cent. The pressure in this vessel decreased from 90/36 to 75/30 mm. Hg.



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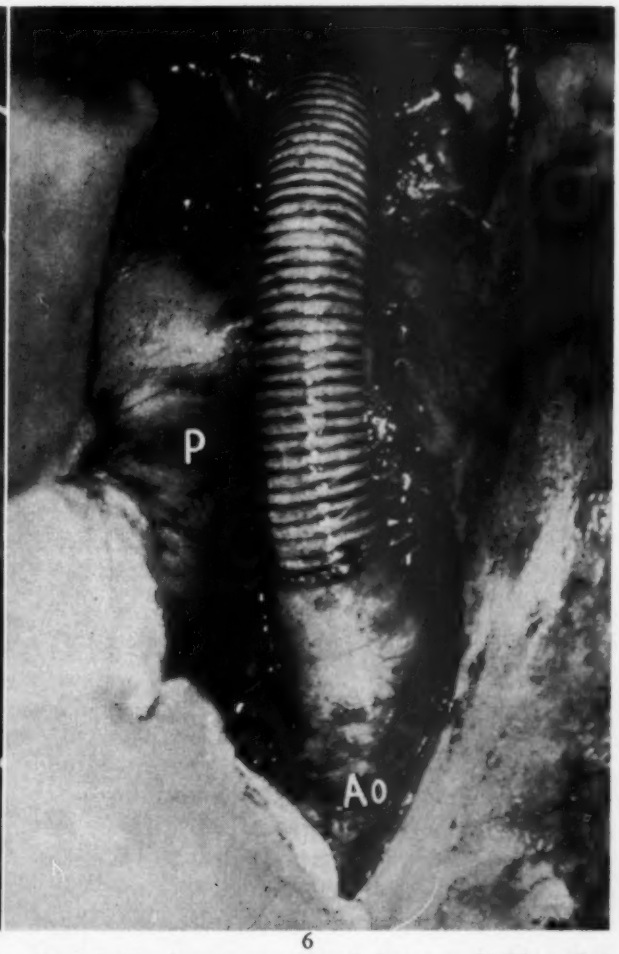

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FIG. 5. Photograph showing the pulmonary artery (PA) to the left (the largest vessel) and the aorta (AO) pulled with a tape, arising from the pulmonary artery.
FIG. 6. The Teflon graft in place, sutured to the descending aorta below and the subclavian artery above.

Systemic blood pressure 24 hours after surgery was 130/90 mm. Hg in both arms and legs. At the end of the third day mild symptoms of cardiac failure developed but were promptly alleviated with digitalis therapy.

Postoperative Results: The remainder of the postoperative course was uneventful. One month after surgery the pressure in the legs increased, reaching 150/80 mm. Hg; the pressure in the arms remained 135/75 mm. Hg. The blood pressures have been stable for 7 months postoperatively.

Radiologic improvement was noted—the size of the heart was considerably reduced and both ventricles decreased in size (Fig. 1B). The profuse vascularity of the lungs was also reduced; however, the prominence of the pulmonary artery remained unchanged. The shadow of the graft is easily seen above the pulmonary artery arch (Fig. 1B).

The electrocardiogram taken 1 month after surgery revealed few changes when compared to the preoperative tracing. Systolic overloading of the right ventricle diminished.

Physical examination disclosed vigorous arterial pulsations in the neck and suprasternal region, a grade 2 systolic thrill over the right carotid artery and a grade 1 systolic thrill over the left carotid artery. The apical impulse was now at the fifth left intercostal space and its impulse was about 2 cm. in area. At this site there was a grade 1 systolic murmur transmitted to the left axilla. Nothing abnormal was noted in the epigastrium. A basal systolic thrill, maximal over the third right intercostal space, and a grade 1 systolic murmur in the midprecordial area remained.

Comment

In reviewing the medical literature in relation to the occurrence of this congenital anomaly,[10–12,17,20,21,25] it was found that only two other patients had undergone surgery. The patient described by Merril et al.[19] in 1955 survived 6 months. The second surgical case was reported by Quie et al;[22] the patient died 2 days after operation.

The patient reported herein underwent surgery on February 18, 1960, and at the present time is in excellent general condition.

Summary

We have studied the case of a 14 year old boy with complete interruption of the aortic isthmus associated with patent ductus arteriosus and probable ventricular septal defect. Surgical correction of the interruption of the aorta was achieved by anastomosing a Teflon prosthesis from the left subclavian artery to the distal aorta.

As far as we know, this patient has had the longest survival with good operative results of any other reported case.

References

1. Abbott, M. E. Atlas of Congenital Cardiac Disease, p. 20. New York, 1936. American Heart Association.
2. Abbott, M. E., Osler, W. and McCrea, T. Modern Medicine, ed. 3, Vol. 4, Philadelphia, 1927.
3. Abrams, H. L. Persistence of fetal ductus function after birth. *Circulation*, 28: 206, 1958.
4. Barger, J. D., Creasman, R. W. and Edwards, J. E. Bilateral ductus arteriosus associated with interruption of the aortic arch. *Am. J. Clin. Path.*, 24: 441, 1954.
5. Currarino, G., Edwards, F. K. and Kaplan, S. Hypoplasia of the left heart complex. *J. Dis. Child.*, 97: 843, 1959.
6. Donzelot, E. Traite des Cardiopathies Congenitales. Paris, 1954. Masson et cie.
7. Dorney, E. R., Fowler, N. O. and Mannaix, E. P. Unilateral clubbing of the fingers due to absence of the aortic arch. *Am. J. Med.*, 18: 150, 1955.
8. Evans, W. Congenital stenosis (coarctation), atresia, and interruption of the aortic arch (a study of 28 cases). *Quart. J. Med.*, 2: 1, 1933.
9. Espino-Vela, J., Acosta, R. A. and de la Cruz, M. V. Interrupcion completa del istmo aórtico. *Arch. Inst. Cardiol.*, 19: 53, 1959.
10. Espino-Vela, J. Malformaciones Cardiovasculares Congénitas. 1959. Inst. Nacional de Cardiologia.
11. Everts-Suárez, E. A. and Carson, P. C. The triad of congenital absence of aortic arch, patent ductus arteriosus and interventricular septal defect. *Ann. Surg.*, 150: 153, 1959.
12. Fournier, P. and Zaidi, Z. H. Congenital absence of the aortic arch. *Am. Heart J.*, 59: 148, 1960.
13. Gaspar, I. Two of the rarer congenital anomalies of the heart. *Am. J. Path.*, 5: 285, 1929.
14. Hamburger, L. P. Congenital cardiac malformation with complete interruption of isthmus aortae and transposition of great arteries. *Bull. Johns Hopkins Hosp.*, 61: 421, 1937.
15. Jew, E. W., Jr. and Gross, P. Aortic origin of the right pulmonary artery and absence of the transverse aortic arch associated with patency of interventricular septum and ductus arteriosus. *Arch. Path.*, 53: 191, 1952.
16. Kinter, E. P. Congenital malformation of the heart: interruption of the aortic arch, mitral valve orifice atresia, and persistent left superior vena cava. *Lab. Invest.*, 2: 388, 1953.
17. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease. p. 448. Chicago, 1955. The Year Book Publishers.
18. Leettrer, E. Kongenitaler Defekt des Aortenbogns. *Centralbl. allg. Path. u. Path. Anat.*, 33: 155, 1923.
19. Merril, D. L., Webster, C. A. and Sanson, P. C. Congenital absence of the aortic isthmus. *J. Thoracic Surg.*, 33: 311, 1957.
20. Noonan, J. A. and Nadas, A. S. The hypoplastic left heart syndrome. *Pediat. Clin. North America*, 5: 588, 1958.

21. NADAS, A. S. Pediatric Cardiology, p. 378. Philadelphia, 1957. W. B. Saunders.
22. QUIE, P. G., NOVICK, R., ADAMS, P., JR., ANDERSON, R. C. and VARCO, R. L. Congenital interruption of the aortic arch. *J. Pediat.*, 54: 87, 1959.
23. SEIDEL, J. F. Index Musei anatomici Kiliensis, p. 61. Kilie, 1818. C. F. Mohr.
24. STEWART, M. Congenital interruption of the aortic arch. *Arch. Dis. Child.*, 23: 326, 1948.
25. SOULIÉ, P. Cardiopathies Congenitales, p. 277. Paris, 1956. L'Expansion Scientifique Francaise
26. TAUSSIG, H. B. Congenital Malformation of the Heart. p. 246. New York, 1960. The Commonwealth Fund.
27. WEISMAN, D., KESTEN, H. D. and PLAINS, W. Absence of transverse aortic arch with defects of cardiac septums. *Am. J. Dis. Child.*, 76: 326, 1948.
28. ZIMMERMAN, H. A. Intravascular Catheterization, p. 178. Springfield, Ill., 1959. Charles C Thomas.

Hemorrhagic Rheumatoid Pericarditis*

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THE HIGH INCIDENCE of fibrinous and fibrous pericarditis associated with rheumatoid arthritis has been consistently documented in autopsy studies.[1–5] We found only one report in the literature of hemorrhagic pericarditis as a systemic manifestation of rheumatoid arthritis.[6] In this patient and the one reported herein fatal cardiac tamponade developed, therefore emphasizing the need for awareness of this rare but clinically significant occurrence.

CASE REPORT

A 50 year old white housewife in acute pulmonary edema was admitted to The Mount Sinai Hospital on December 28, 1959. Five days prior to admission, following the sudden illness of her husband, she became extremely anxious and, during the next few days, pulmonary edema developed. Steroids taken over the past six years for rheumatoid arthritis were discontinued the day prior to admission.

Past History: The patient had been hospitalized in 1938, having had for five months intermittent pain, swelling and limitation of motion of the wrist, metacarpal and proximal interphalangeal joints spreading to the ankle, knee, hip, shoulder and temperomandibular joints. Physical examination at that time revealed slightly swollen, warm, tender joints and both a blowing systolic and rough presystolic apical murmurs. The heart was not enlarged. These cardiac findings were similar to those noted one year previously when a parotid tumor was removed. Over the next six years she was readmitted five times for exacerbations of rheumatoid arthritis. During this period multiple subcutaneous nodules and splenomegaly developed. The heart murmurs persisted. She was admitted to various other hospitals for similar complaints over the next thirteen years. Steroid therapy was begun in 1953. In May 1958 she was admitted to Mount Sinai Hospital with a cough, fever and right-sided pleuritic chest pain. Significant physical findings at this time were rales at the base of the right lung, a grade 3 apical systolic murmur and a presystolic rumble, a loud snapping first sound, P_2 louder than A_2, typical chronic rheumatoid joint deformities, subcutaneous nodules over extensor surfaces and bilateral episcleritis. Roentgenographic examination of the chest (Fig. 1A) showed blunting of the right costophrenic angle and a poorly defined infiltration in the right middle lobe. The electrocardiogram (Fig. 2A) was suggestive of acute pericarditis. She improved on conservative management and was discharged seven days later. Until her last admission, she had never had signs or symptoms of heart failure.

Physical examination (after initial treatment of pulmonary edema) disclosed a blood pressure of 105/70 mm. Hg, regular pulse rate of 138, respirations 24 and temperature 100.6°F. Classic chronic rheumatoid joint deformities, subcutaneous nodules over the extensor surfaces of the extremities, bilateral episcleritis, and apical systolic and presystolic murmurs were again noted. The heart was enlarged with the point of maximal impulse at the anterior axillary line. Bilateral basilar rales were present. Pertinent laboratory data included: sedimentation rate, 38 mm./hr.; total protein, 6.7 with albumin/globulin ratio of 3.0/3.7; serum glutamic oxaloacetic transaminase, 30; C-reactive protein 2+; antistreptolysin titer, 125 units; and lupus erythematosus cell preparation was negative. The electrocardiogram revealed atrial flutter with 2:1 block.

Hospital Course: Initial treatment included deslanoside, morphine and mercurial diuretics. Over the next few days the following developed: a pericardial friction rub, severe joint pains, tachycardia, splenomegaly and red macular patches over the extremities. Repeated blood cultures were negative. Chest roentgenogram on January 7, 1960 (Fig. 1B), showed bilateral thickened pleurae and an enlarged heart. A repeat electrocardiogram (Fig. 2B) revealed digitalis effect and persistent atrial flutter. On the sixteenth hospital day dyspnea suddenly developed, the friction rub disappeared, heart sounds diminished, and marked hepatomegaly, and hepatojugular reflux, basilar rales and leg edema developed. The venous pressure was 220 mm. H_2O. She became hypotensive and died several hours later.

AUTOPSY

Gross Findings: Numerous subcutaneous nodules were present over the extensor surfaces of the extremities. Multiple fibrous adhesions were noted over both lung surfaces. The pericardial sac was markedly distended, tense, bulging, and blue in appearance. The heart could be balloted in this

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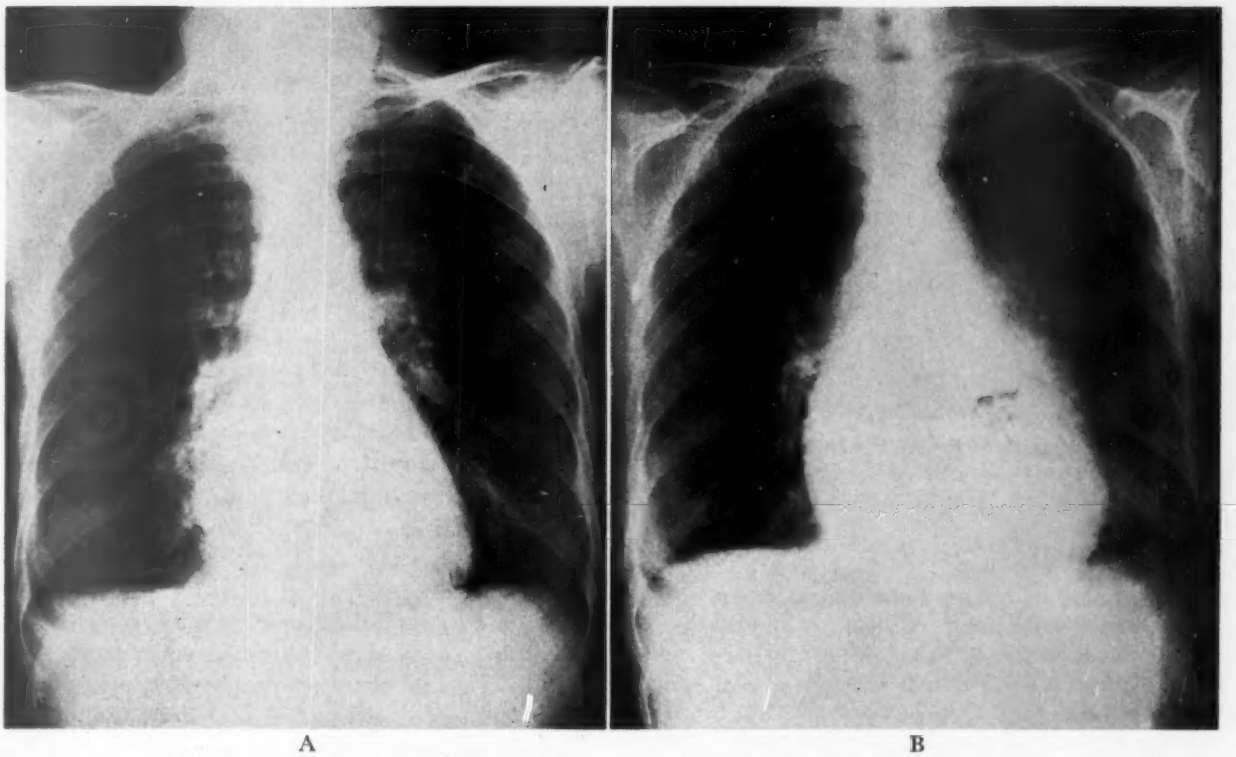

A B

FIG. 1. Chest x-ray films. A, May 1958. Poorly defined infiltration adjacent to the right border of the heart. Blunting of the right costophrenic angle. The heart is somewhat large and shows localized prominence of the left border in the supraventricular segment apparently due to enlargement of the left atrial appendage. Slight rounding of the ventricular apical region. B, January 6, 1960 (10 days after final admission). Blunting of the right costophrenic angle. The heart has a globular configuration. There is a double density along the upper left border of the heart and a localized prominence at the level of the left atrial appendage.

sac. On incising the pericardium approximately 350 cc. of red-brown blood gushed out under pressure. The epicardium and pericardium were coated by a shaggy tan-brown material which was easily removed by scraping (Fig. 3). The left atrium was markedly, and the right atrium moderately, dilated. A "fish-mouth" type mitral stenosis was present, barely admitting a fingertip. The valve was thickened, scarred and focally calcified. The chordae tendineae were short and fused. The leaflets of the tricuspid

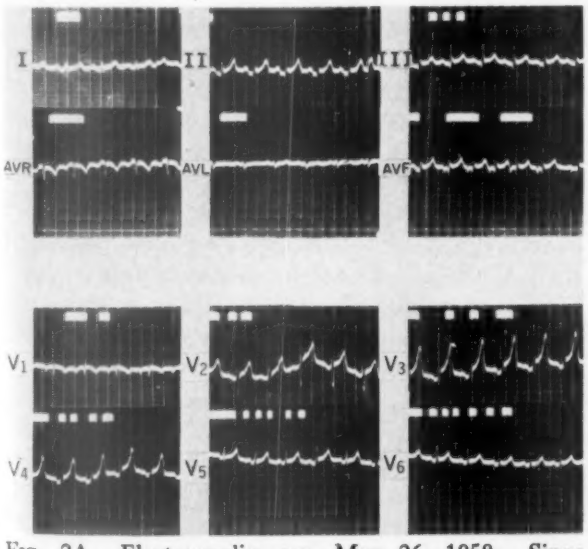

FIG. 2A. Electrocardiogram, May 26, 1958. Sinus arrhythmia averaging 105 per minute with wandering pacemaker. Notched P wave. S-T segment elevation in leads II, III, aVF, and V_2 to V_6. T wave peaked in V_2 to V_4 with high voltage in V_3.

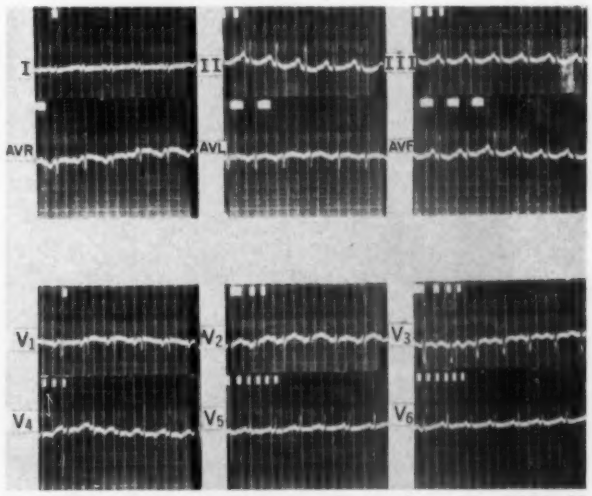

FIG. 2B. Electrocardiogram, December 30, 1959 (2 days after final admission). Sinus tachycardia, rate 107 per minute. Nonspecific S-T segment and T wave changes; possible digitalis effects.

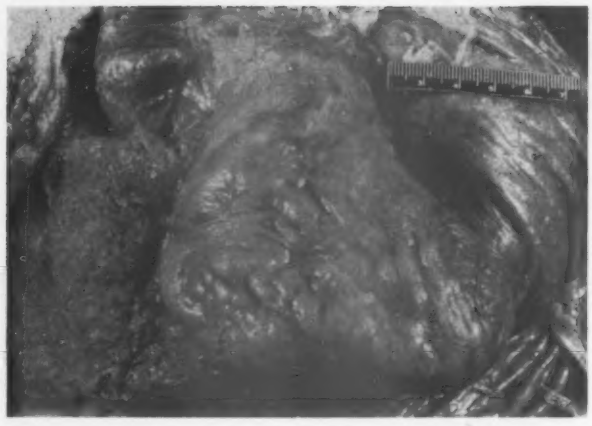

FIG. 3. Photograph of heart at autopsy after incision and retraction of pericardium. Note the shaggy exudate on the epicardial and parietal pericardial surfaces.

and pulmonic valves, and the endocardium of the left atrium were scarred minimally. There were no valvular vegetations. The left atrium and right ventricle were slightly hypertrophied. The myocardium appeared within normal limits. The splenic and renal capsules revealed focal patchy fibrosis. The viscera were congested.

Microscopic Examination: The epicardium was covered by several layers. The superficial one consisted of fibrin, nuclear debris and acute inflammatory cells. The deeper one was composed of fibrin with early organization and a cellular exudate of plasma cells, lymphocytes and occasional foreign body giant cells. The myocardium failed to show recent or old Aschoff's bodies. The subcutaneous nodules were of the well known rheumatoid type. A piece of the joint obtained by small incision revealed chronic inflammation. The lungs showed moderate chronic congestion and edema.

Comments: This patient's conspicuous mitral stenosis did not cause symptomatic heart disease until her acute anxiety episode. When pulmonary edema developed, therapy with steroids she had been taking for six years was discontinued. Several days later, an acute exacerbation of systemic rheumatoid arthritis developed, with hemorrhagic pericarditis and cardiac tamponade, and the patient died.

COMMENTS

The previously reported case of hemorrhagic pericarditis as a systemic manifestation of rheumatoid arthritis is similar to the case presented herein. The patient reported earlier was a 52 year old woman who had a long history of rheumatoid arthritis with episodes of pleuritic and precordial pain. The withdrawal of steroids resulted in exacerbation. Her terminal admission followed also a short period of steroid withdrawal. A flare-up of the rheumatoid disease resulted, and acute right heart failure and shock developed. Autopsy revealed a pericarditis with a hemopericardium of 350 cc. and pleuritis. Microscopic examination of the pericardium showed a fibrinous exudate overlaying a layer of granulation tissue with a cellular exudate similar to that in our case including numerous large multinucleated giant cells.

The incidence of pericarditis as an autopsy finding in patients with rheumatoid arthritis is significantly high. The frequency of this association was noted as early as 1904 by Barié.[7] Graef,[2] in his series of sixty-six hearts from patients with rheumatoid arthritis, found thirty-three cases of pericarditis. Young and Schwedel[5] discovered nineteen case of pericarditis in their series of thirty-eight autopsies of rheumatoid cases. Egelius et al.[1] collected 439 autopsy reports from seven series of autopsies of patients who had rheumatoid arthritis and noted pericarditis in 133 cases, an incidence of 31 per cent. In an exacting study by Sokoloff,[4] pathologic material from autopsies of 101 patients who had rheumatoid arthritis was examined and the findings compared with those in 1,154 control autopsies. The incidence of pericarditis in the cases of rheumatoid arthritis was 40.6 per cent, whereas the incidence in the control series was 8.8 per cent. The patients in these series had chronic deforming rheumatoid arthritis of long-standing with typical clinical, roentgenologic and laboratory findings.

Pathologically, in the large majority of these cases the pericarditis was fibrous adhesive or obliterative. A few patients had acute fibrinous pericarditis, occasionally with a granulomatous inflammation. In only few of the cases observed did the pericardium show histologically the lesion found in subcutaneous nodules of rheumatoid arthritis[8–12] which is the only specific lesion. These are cases of severe systemic rheumatoid arthritis with lesions in some or all of the following locations: myocardium, heart valves, dura, splenic capsule, lung, pleura, peripheral nerves, sclerae, esophagus and skeletal muscle. Acute fibrinous pericarditis is found in patients who die during an acute flare-up of systemic rheumatoid arthritis. Fibrous pericarditis is found in patients with chronic rheumatoid arthritis who die from an unassociated coexisting disease. Therefore, it has

been suggested that the fibrinous pericarditis represents a "burned-out" acute rheumatoid pericarditis.[4]

At least two reports in the literature record pericardial effusion complicating rheumatoid pericarditis. In one case[10] 200 cc. of fluid removed during life contained many polymorphonuclear leukocytes and a few lymphocytes. Cultures for pyogenic and tubercular organisms were negative. At autopsy fibrinous pericarditis with 100 cc. of cloudy fluid and widespread systemic rheumatoid nodules were found. The other case,[13] we believe, is one of acute benign pericarditis in a patient with chronic rheumatoid arthritis, because of the typical history, clinical course and absence of other manifestations of a rheumatoid flare-up. A case of chronic constrictive pericarditis in a patient with rheumatoid arthritis is considered by us to be probably of fungal or tubercular cause as calcifications were noted in the pericardium and adrenals.[14]

Discussion of the other systemic manifestations of rheumatoid arthritis in this case, episcleritis[15] and pleuritis[16–18] and of valvular heart disease as related to rheumatoid arthritis[2–5,12,19–21] is beyond the scope of this paper. However, a question may arise concerning the etiology of the pericarditis since rheumatic mitral stenosis was present. It is our belief that a rheumatic origin is not likely for the following reasons: (1) The patient had long-term active rheumatoid arthritis with frequent rheumatoid flare-ups. The chronic joint picture she presented is not found in rheumatic fever. (2) Rheumatoid flare-up following steroid withdrawal is common. (3) The pericarditis which followed steroid withdrawal was associated with a systemic flare-up of her previous rheumatoid signs and symptoms. (4) No Aschoff's bodies were found in the myocardium which was also otherwise normal. (5) A normal antistreptolysin titer was present. (6) The finding of mitral stenosis is, of course, characteristic of chronic rheumatic heart disease and not acute rheumatic fever.

Summary

A case of hemorrhagic pericarditis as a systemic manifestation of rheumatoid arthritis is described which is apparently the second reported. Pericarditis is a frequent autopsy finding in rheumatoid arthritis. It represents a rare cause of death which developed in both instances following the withdrawal of steroids.

Addendum

Since preparation of this manuscript Nadas and Levy[22] have reported on five children with rheumatoid pericarditis. One child who died during the episode associated with pericarditis had 300 cc. of blood in the pericardial sac at autopsy. However, this child had hemorrhagic manifestations, including a profuse nosebleed and hematemesis, twenty-four hours before death.

References

1. Egelius, N., Göhle, O., Jonsson, E. and Wahlgren, F. Cardiac changes in rheumatoid arthritis. *Ann. Rheumat. Dis.*, 14: 11, 1955.
2. Graef, I., Hickey, D. V. and Altmann, V. Cardiac lesions in rheumatoid arthritis. (Abstract) *Am. Heart J.*, 37: 635, 1949.
3. Sinclair, R. J. G. and Cruikshank, B. A clinical and pathological study of sixteen cases of rheumatoid arthritis with extensive visceral involvement ("rheumatic disease"). *Quart J. Med.*, 25: 313, 1956.
4. Sokoloff, L. The heart in rheumatoid arthritis. *Am. Heart J.*, 45: 635, 1953.
5. Young, D. and Schwedel, J. B. The heart in rheumatoid arthritis: a study of thirty-eight autopsy cases. *Am. Heart J.*, 28: 1, 1944.
6. Bevans, M., Nadell, J., Demartini, F. and Ragan, C. The systemic lesions of malignant rheumatoid arthritis. *Am. J. Med.*, 16: 197, 1954.
7. Barié, E. Le coeur dans le rhumatisme chronique. *Arch. gén. med.*, 2: 2881, 1904.
8. Clark, W. S. and Bauer, W. Cardiac changes in rheumatoid arthritis. (Abstract) *Ann. Rheumat. Dis.*, 7: 39, 1948.
9. Ellman, P., Cudkowicz, L. and Elwood, J. S. Widespread serous membrane involvement by rheumatoid nodules. *J. Clin. Path.*, 7: 239, 1954.
10. Maher, J. A. Dural nodules in rheumatoid arthritis: report of a case. *Arch. Path.*, 58: 254, 1954.
11. Raven, R. W., Weber, F. P. and Price, L. W. The necrobiotic nodules of rheumatoid arthritis. *Ann. Rheumat. Dis.*, 7: 63, 1948.
12. Rosenberg, E. F., Baggenstoss, A. H. and Hench, P. S. The causes of death in thirty cases of rheumatoid arthritis. *Ann. Int. Med.*, 20: 903, 1944.
13. Granirer, L. W. Pericardial effusion in rheumatoid arthritis. *M. Clin. North America*, 30: 562, 1946.
14. McMurray, C., Cayer, D. and Cornatzer, W. E. Chronic adhesive pericarditis due to the rheumatic state, associated with liver damage, serous effusions, and pigmentation. *Gastroenterology*, 17: 294, 1951.
15. Goar, E. L. and Smith, L. S. Rheumatoid nodules of the eye. *J. A. M. A.*, 148: 889, 1952.
16. Bloom, J. and Rubin, J. H. Transient pulmonary manifestations in rheumatoid arthritis. *Canad. M. A. J.*, 63: 355, 1950.
17. Horler, A. R. and Thompson, M. The pleural and pulmonary complications of rheumatoid arthritis. *Ann. Int. Med.*, 51: 1179, 1959.
18. Leys, D. G. and Swift, P. N. Pulmonary lesions in rheumatoid arthritis. *Brit. M. J.*, 1: 434, 1949.
19. Baggenstoss, A. H. and Rosenberg, E. F. Unusual

cardiac lesions associated with chronic multiple rheumatoid arthritis. *Arch. Path.*, 37: 54, 1944.

20. Baggenstoss, A. H. and Rosenberg, E. F. Visceral lesions associated with chronic infectious rheumatoid arthritis. *Arch. Path.*, 35: 503, 1943.
21. Bayles, T. B. Rheumatoid arthritis and rheumatic heart disease in autopsied cases. *Am. J. M. Sc.*, 205: 42, 1943.
22. Nadas, A. S. and Levy, J. M. Pericarditis in children. *Am. J. Cardiol.*, 7: 109, 1961.

Generalized Glycogenosis*

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MANY CASES of glycogen storage disease of the liver and kidney (Von Gierke's disease) have been described and the enzyme defect, absence of glucose-6-phosphatase, has been known since 1952.[1] The glycogen is structurally normal.

Four other types of glycogenosis due to enzyme deficiencies are known. Lack of the brancher enzyme, amylo-1,4 → 1,6-transglucosidase, has been implicated in one case of glycogenosis involving the liver, spleen, lymph nodes and intestinal mucosa (diffuse glycogenosis with hepatic cirrhosis). The glycogen structure in this disease is structurally abnormal, having fewer branch points and long inner and outer chains resembling amylopectin.[2]

Deficiency of the debrancher enzyme, amylo-1,6-glucosidase, has been found in cases with glycogen deposition in liver and skeletal muscle.[2] In this disorder the glycogen has increased branch points and short outer chains like phosphorylase limit dextrin.

An isolated skeletal muscle type of glycogenosis due to virtual absence of phosphorylase[3,4] and an isolated hepatic type due to diminution of phosphorylase[5] have been described.

Generalized glycogenosis (heart, skeletal muscle, liver) has been reported, in frequency second only to Von Gierke's disease, but opportunities for enzymatic as well as clinical, pathologic and chemical studies have been infrequent. For this reason a patient with generalized glycogenosis in whom enzyme studies were performed is reported.

CASE REPORT

History: A 4 month old Negro boy was admitted on June 12, 1958 with symptoms of poor sucking, poor gain of weight and muscle weakness. The infant was the product of a full term pregnancy during which the mother complained of excessive nervousness and frequent stomach pains. Labor and delivery were not remarkable. The infant was born on February 17, 1958 weighing 8 pounds 14 ounces. For the first month of life frequent greenish, watery stools were noted. At $1^1/_2$ months his cry was weak, he had gained weight poorly, his arms and legs were very "limber," and he did not move or kick vigorously. Poor sucking, gagging and choking during feedings were noted at 3 months of age and continued until admission to the hospital.

Family History: Six male children from the mother's first marriage were in good health. The patient was a product of the second marriage from which there were two siblings, a 6 year old girl who was in good health and a male infant who had had a remarkably similar history of marked muscle weakness, dysphagia and died at age 5 months. No postmortem examination was performed on this infant. No other relatives were known to have muscle weakness, swallowing difficulties or heart trouble.

Physical Examination: Inspection revealed a weak, listless 4 month old Negro male infant who appeared wasted and chronically ill. The facies was dull, the cry weak and the tongue large and protruding. The weight was 5.1 kg. (normal weight at age 2 months), length 63 cm. (normal height at age 5 months), head circumference 40.5 cm., temperature 98°F. rectally, respirations 40 per minute, pulse 160 per minute and blood pressure in the right arm by the flush method 90 mm. Hg. An excessive amount of secretions was present in the nose and oropharynx, and coarse inspiratory rales were heard over the lung fields. Cardiac size, rate and rhythm were within normal limits. A harsh, grade 3 systolic murmur was present at the second, third and fourth left intercostal spaces parasternally. The liver was palpable 5 cm. below the right costal margin. In the prone position he could not lift his chin or chest. Movements of the extremities were greatly diminished, the muscles were flaccid but not atrophic and the deep tendon reflexes were absent

Laboratory Findings: Hemogram, cephalin cholesterol flocculation, thymol turbidity, total serum pro-

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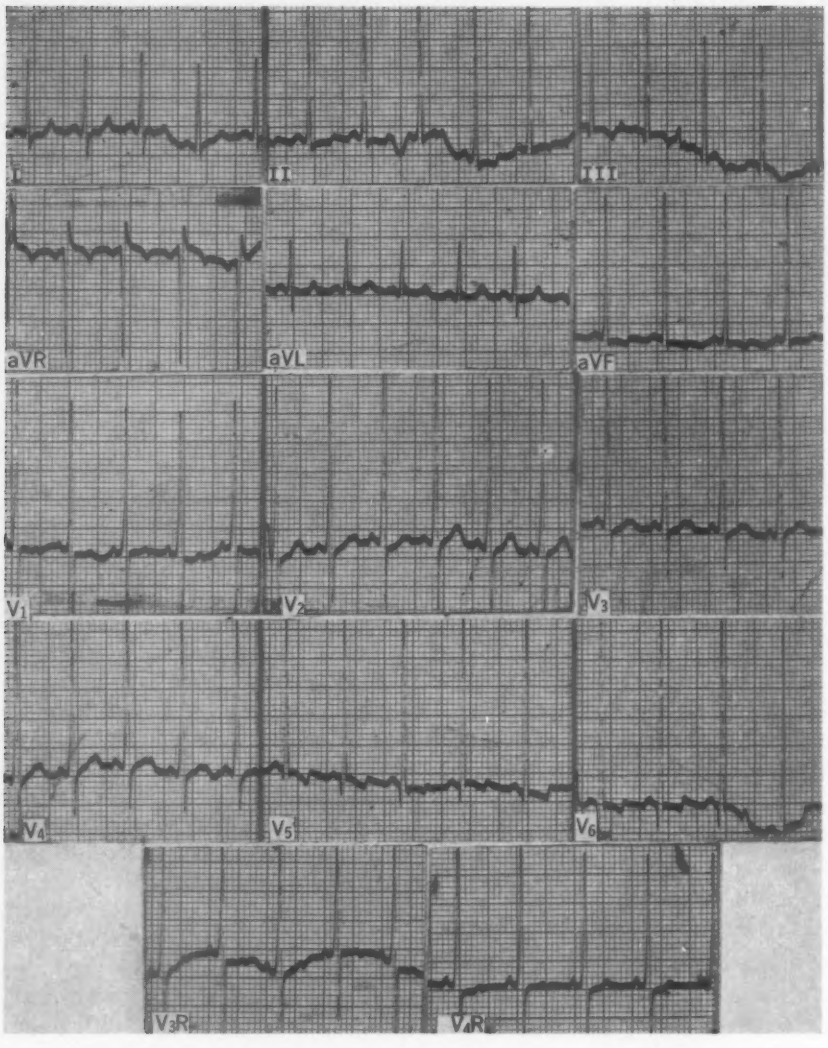

FIG. 1. Electrocardiographic tracing on June 13, 1958.

teins, albumin and globulin ratio, fasting blood sugar, prothrombin time, alkaline phosphatase, serum bilirubin, serum sodium, potassium, chlorides, carbon dioxide combining power, calcium, phosphorus, sweat chlorides, and total fatty acids were within normal limits. Urinalyses were normal except for 1+ proteinuria. The protein bound iodine was 3.8 μg. per cent (normal for this laboratory 4 to 8 μg. per cent). Oral glucose tolerance test was as follows: fasting 61 mg. per cent, $^1/_2$ hour 76 mg. per cent, 1 hour 73 mg. per cent, $1^1/_2$ and 2 hours 69 mg. per cent, 3 hours 76 mg. per cent.

Radiographic Examinations: Roentgenogram of the chest on June 13, 1958 revealed cardiac enlargement with a boot shaped contour. Repeat x-ray examination of the chest on August 7, 1958 showed generalized cardiomegaly and consolidation of part of the upper portion of the right lung. Angiocardiogram performed on July 18, 1958 was noncontributory.

Electrocardiograms: June 13, 1958. The rate was 140 per minute; P-R interval, 0.09 second; QRS, 0.08 second; Q-T 0.28 second; and QRS axis plus 70°. The precordial leads showed evidence of right and left ventricular hypertrophy and deep Q waves in V_5 and V_6 suggesting septal hypertrophy. The T waves were inverted in leads III, aVF, V_5 and V_6 (Fig. 1).

July 11, 1958. The QRS axis shifted to plus 85°, a deep S developed in leads I, aVL, V_5 and V_6 and the T waves in leads III, aVF, V_5 and V_6 were now upright. Digitalis effects were present (Fig. 2).

September 5, 1958. The QRS axis shifted to plus 130° and slight S-T segment elevations in V_2-V_6 suggested subepicardial injury. Signs of ventricular hypertrophy were unchanged.

Biopsy of the Gastrocnemius Muscle: Considerable fragmentation and vacuolization of muscle fibers were noted on the hematoxylin and eosin preparations. A large amount of PAS positive material was present. After diastase digestion and restaining with PAS the number of PAS positive granules was greatly reduced.

Clinical Course: The patient continued to have

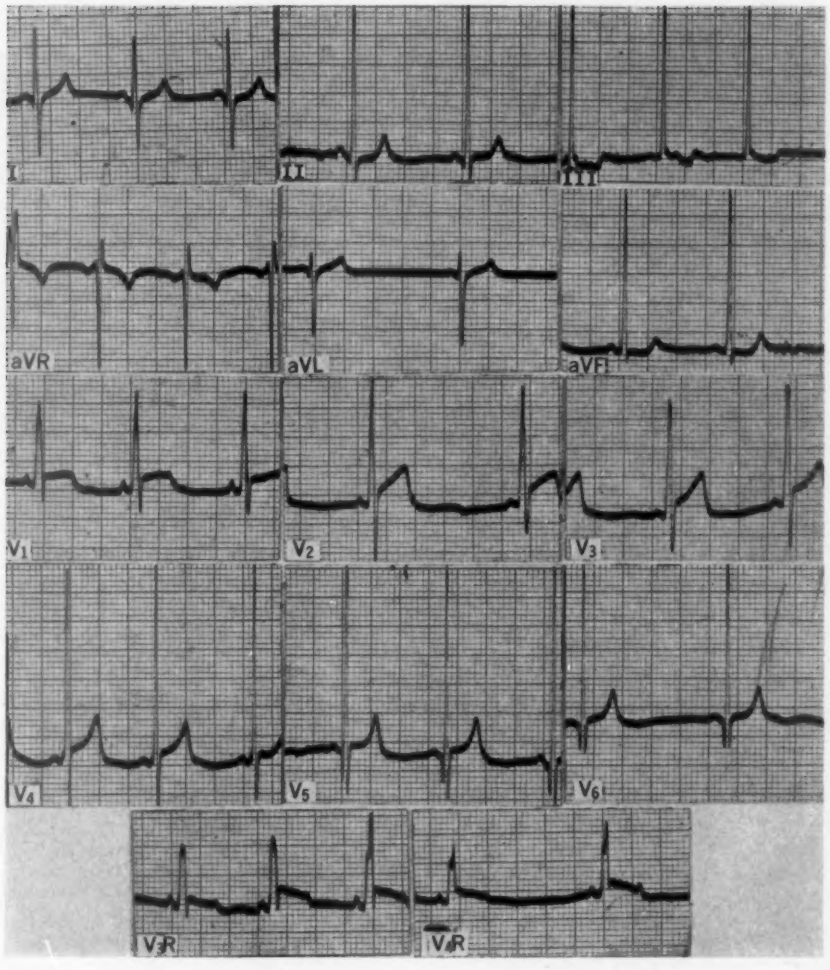

FIG. 2. Electrocardiographic tracing on July 11, 1958.

generalized muscle weakness, loose foul stools, gagging during feedings, pooling of oral secretions and sucked poorly. He seemed too weak to handle his secretions. Cardiac catheterization and angiocardiography were performed and did not reveal any definite abnormalities. On July 30, 1958 his temperature rose to 104°F. rectally. There were slight grunting respirations, flaring of the ala nasi and slight costal retractions. He was treated supportively with tube feedings, multiple antibiotics, digitalis and gamma globulin without improvement. He failed to gain weight, his condition gradually deteriorated and he died on September 10, 1958, at 7 months of age after 3 months of hospitalization.

Pathologic Findings: The postmortem interval was 2 hours. Tissues were fixed in absolute alcohol, Carnoy's fluid and 10 per cent buffered formalin. The material was stained with hematoxylin and eosin, PAS and Best's carmine. Tissues were incubated in diastase for 30 minutes for control.

Heart. The heart weighed 120 gm. (four times normal weight). The thickness of the right ventricle was 0.5 cm.; that of the left, 1.1. cm. The epicardium was smooth and glistening, the myocardium firm and pale brown, the endocardium thin and shiny. All valves were delicate and competent. No congenital defects were noted. Sections of myocardial tissue revealed marked vacuolization. Some of the muscle bundles were so full of fine granular material that the nuclei were pushed to one side. Other bundles were only partly involved; a few were essentially normal. This vacuolar material was strongly PAS positive and was almost entirely removed by diastase digestion (Fig. 3A).

Liver. The liver weighed 315 gm. Sections stained with hematoxylin and eosin revealed characteristic fine granularity of the cytoplasm and, to a lesser degree, of the nuclei. The parenchymal cells were markedly positive for PAS staining material, which was almost entirely removed by diastase digestion (Fig. 3B).

Skeletal muscle. The muscles were pale pink, firm and slightly atrophic. The tongue was large, measuring 6.0 by 2.5 by 1.2 cm. Marked vacuolization and fragmentation of muscle fibers were present. Most of the sarcoplasm was pushed to one side by the vacuolizations. The material in the vacuoles was intensely positive for PAS and was virtually removed

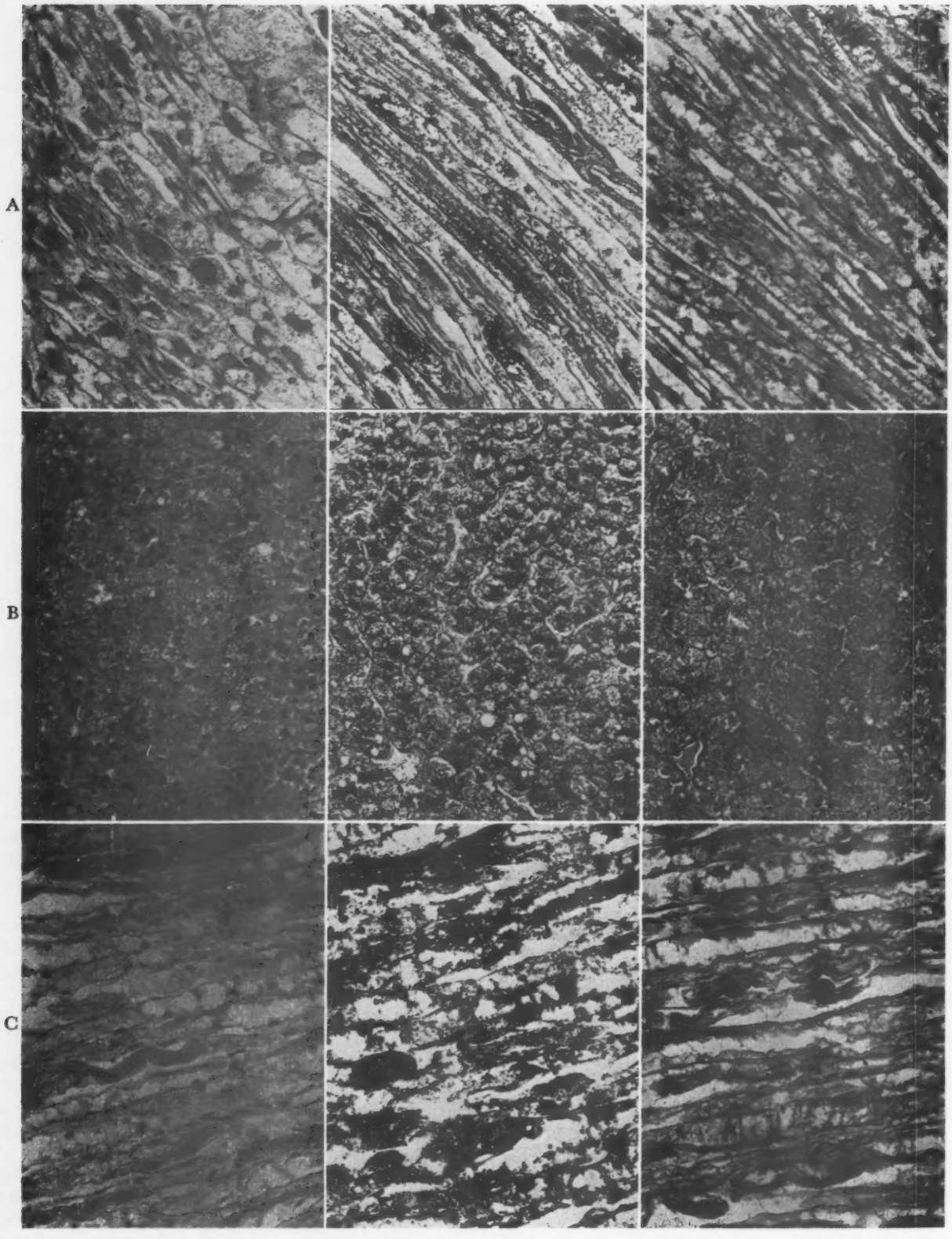

FIG. 3. Demonstration of glycogen by histochemical technics. A, cardiac muscle; B, liver; C, skeletal muscle. *Left column*, stained with hematoxylin and eosin; *middle column*, stained with periodic acid-Schiff; *right column*, diastase digestion after periodic acid-Schiff staining.

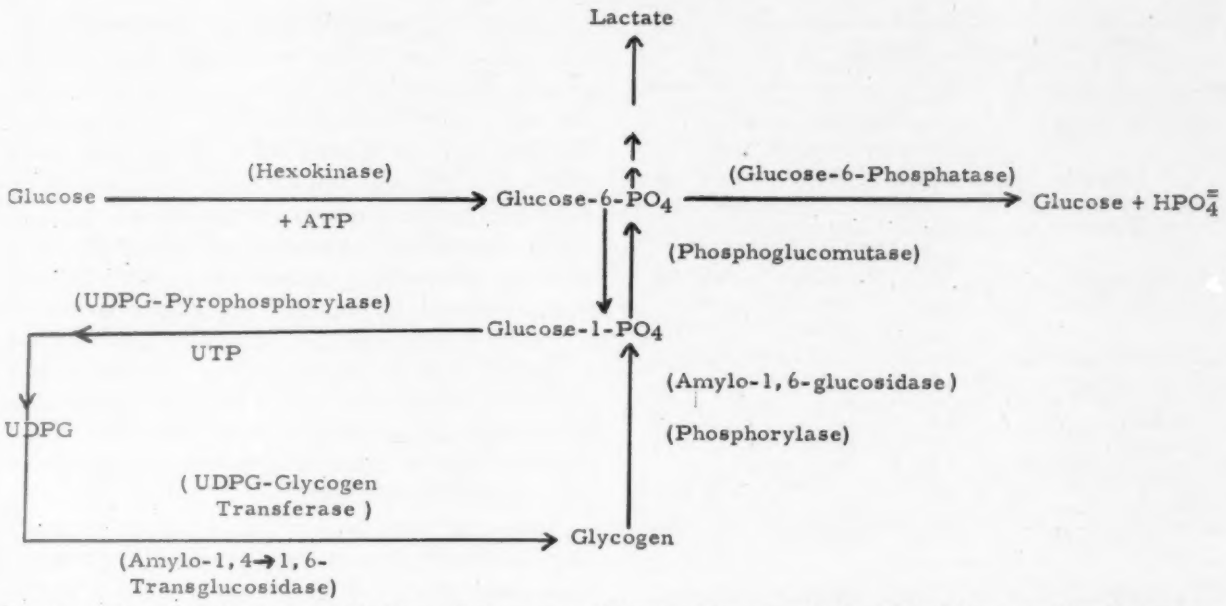

FIG. 4. Scheme of glycogen metabolism. Enzymes are designated by parenthesis. The following abbreviations are used in this diagram: ATP, adenosine triphosphate; UTP, uridinetriphosphate; and UDPG, uridinediphosphate glucose.

after diastase digestion (Fig. 3C). Skeletal muscle other than the tongue was involved to a lesser extent.

Brain. The brain weighed 753 gm. Multiple cross sections of the cerebrum and brainstem appeared normal. The brain demonstrated immature development with a persistent outer granular layer over the cerebellum which was about two cell layers thick. Sections were studied in a variety of preparations in attempt to identify abnormal storage material within the neurons; Nissls method, hematoxylin and eosin, PAS, Luxol fast blue, Sudan III, Oil-red-O and Lorrain Smith-Dietrich stains were made. These sections showed large neurons the cytoplasm of which was two to three times normal size. No Nissl substance was present in most of the enlarged parts of the cytoplasm. The neurons resembled those in amaurotic familial idiocy; however, no lipids or lipoids were demonstrated. A small amount of PAS-positive material found in many of these enlarged neurons indicated glycogen deposition. The neurons most involved in this storage disease were those of the medulla and upper part of the brainstem. The greatest involvement was seen in the hypoglossal nucleus, dorsal motor nucleus of the vagus and vestibular nuclei. There was lesser involvement of the inferior olivary bodies, Purkinje cells and dentate nuclei. The cells of the cerebral cortex were not particularly involved.

Lungs. The lungs weighed 65 gm. Widespread atelectasis and large foci of hemorrhage were present grossly and microscopically.

Kidneys. The kidneys weighed a total of 85 gm. (twice normal size), but were otherwise grossly normal. PAS stains revealed a slight nonspecific thickening of the basement membranes of many glomerular tufts. This PAS positive material was not changed with diastase digestion. Many of the tubular epithelium cells had a peculiar clear vacuolization of cytoplasm with hematoxylin and eosin, but failed to contain any significant PAS positive material. The remainder of the postmortem examination including the gastrointestinal tract, endocrine organs, spleen and lymphatics was normal grossly and microscopically.

Tissue glycogen studies. A portion of the premortem skeletal muscle biopsy and postmortem tissue from the heart, liver and skeletal muscle were collected and frozen. Specimens were sent in a frozen state to the Department of Biological Chemistry at Washington University School of Medicine. Glycogen determinations were carried out separately at the Washington University Laboratory and Research Laboratory of the Department of Pediatrics, University of Texas Medical Branch (Table I). An autoglycogenolysis test was done at the University of Texas laboratory. Glycogen content of these tissues was the same after storage for 24 hours at room temperature.

Enzyme assays (Department of Biological Chemistry, Washington University School of Medicine).[6] The structural analysis of glycogens was within normal limits. Thirty-eight to 40 per cent of the total glycogen was digested after the addition of recrystallized phosphorylase and purified amylo-1,6-glucosidase (debrancher enzyme). A glucose-6-phosphatase assay revealed 540 gammas of glucose-6-PO4 split per 100 gm. liver per hour. Uridine diphosphoglucose-glycogen transferase was present in cardiac muscle (1.5 units per gm. tissue) and cardiac muscle phosphorylase was 93 units total phosphorylase, 692

TABLE I
Glycogen Analysis

Tissue	Glycogen Levels (gm. per cent net weight)		
	Normal Subject	Patient	
		Washington University	University of Texas
Skeletal muscle			
(biopsy)	1–2	12.1	...
(autopsy)	...	11.6	12.0
Cardiac muscle	...	5.5	6.6
Liver	2–4	9.2	8.8

units phosphorylase A. These enzyme determinations were within normal limits.

COMMENTS

Many clinical and laboratory features distinguish glycogen storage disease of the liver and kidney. The presence of hepatomegaly, hypoglycemia, diminished blood glucose rise following epinephrine, hyperlipemia and acetonemia are characteristic. In generalized glycogenosis confirmatory laboratory tests are lacking. Liver function studies, glucose and galactose tolerance tests, epinephrine tests and blood lipids have been normal. Laboratory studies on this patient were within normal limits except for a flat oral glucose tolerance test. Unfortunately, this was not repeated and an epinephrine test was not performed.

At the present time the diagnosis of generalized glycogenosis during life can be made only by chemical demonstration of significantly increased glycogen in skeletal muscle tissue. Erythrocyte and leukocyte glycogen concentrations in patients with this glycogenosis have been normal although increased quantities of abnormal glycogen were noted in erythrocytes of patients with amylo-1,6-glucosidase deficiency and the abnormal structured glycogen amylopectin has been isolated in the leukocytes of a patient with amylo-1,4 → 1,6-transglucosidase.[7] The histochemical identification of glycogen by PAS staining, diastase digestion and restaining with PAS is specific.[8] The digestion of PAS positive granules by diastase from tissue of this patient is clearly depicted in Figure 3. Increased glycogen levels in the premortem and postmortem tissues of our patient confirmed the diagnosis (Table 1).

Electrocardiographic findings of biventricular and septal hypertrophy were indicative of widespread, uniform involvement and consistent with the report of Friedman and Ash.[9] The cardiac findings were suggestive of a congenital heart lesion, but this was not substantiated by angiocardiogram and cardiac catheterization.

The resemblance to amyotonia congenita was striking. However, generalized glycogenosis was suspected because of the combination of myopathy, macroglossia, cardiomegaly, hepatomegaly and cretinoid facies. Although the cardiac findings were quite prominent, cardiac failure did not occur and death was due to extensive muscle involvement with pulmonary atelectasis and insufficiency.

Attempts have been made to separate cases of generalized glycogenosis into cardiac or skeletal muscle types.[10] The principal areas of glycogen storage in this case were the heart, skeletal muscle (particularly the tongue), liver and brain. No differentiation into a cardiac or a skeletal muscle type seems possible in this patient. Involvement of the central nervous system was confined principally to the midbrain and upper medulla with lesser involvement in the dentate nuclei and Purkinje cells. This distribution is similar to the case of Clement and Godman.[11]

Debrancher enzyme insufficiency has been implicated in generalized glycogenosis in one patient on the basis of ultracentrifugation studies of glycogen,[10] and in two patients with low glucosidase activity and short outer chain glycogen structure.[12] Four other cases of generalized glycogenosis have been reported from the Washington University laboratory revealing normal glycogen structure and normal enzyme assays.[6] Paradoxically, in this case, glycogen structure and enzyme assays were normal but autoglycogenosis did not occur.

The pertinent reactions involved in glycogen formation and degradation are depicted in Figure 4. Examination of this figure and the foregoing data do not provide an explanation for the presence of generalized glycogenosis in this patient.

SUMMARY

A case report of an infant with generalized glycogenosis involving the heart, skeletal muscle, liver and brain is presented. A genetic origin is suggested by the history of a sibling dying at a similar age with the same symptoms. Evidence is presented that glycogen structure and enzyme

determinations were within normal limits but autoglycogenolysis was absent.

Acknowledgment

We are indebted to Barbara Brown, PH.D., of Washington University School of Medicine and Hilda Wiese, PH.D., of the University of Texas, for their assistance in glycogen and enzyme assays. The critical advice of C. W. Daeschner, M.D. and technical assistance of Miss Cecilia Quin were greatly appreciated.

References

1. Cori, G. T. and Cori, C. F. Glucose-6-phosphatase of the liver in glycogen storage disease. *J. Biol. Chem.*, 199: 661, 1952.
2. Illingworth, B. and Cori, G. T. Structure of glycogens and amylopectins. III. Normal and abnormal human glycogen. *J. Biol. Chem.*, 199: 653, 1952.
3. Mommaerts, W. F., Illingworth, B., Pearson, C. M., Guillory, R. J. and Seraydarian, K. A functional disorder of muscle associated with the absence of phosphorylase. *Proc. Nat. Acad. Sc. U. S.*, 45: 791, 1959.
4. Schmid, R., Robbins, P. W. and Traut, R. R. Glycogen synthesis in muscle lacking phosphorylase. *Proc. Nat. Acad. Sc. U. S.*, 45: 1236, 1959.
5. Hers, H. G. Enzymatic studies of hepatic fragments; applications to the classifications of glycogenoses. *Rev. intern. hepat.*, 9: 35, 1959.
6. Hauk, R., Illingworth, B., Brown, D. H. and Cori, C. F. Enzymes of glycogen synthesis in glycogen deposition disease. *Biochim. et biophys. acta*, 33: 554, 1959.
7. Sidbury, J. B., Cornblath, M., Fisher, J. and Hause, E. Glycogen in erythrocytes of patients with glycogen storage disease. *Pediatrics*, 27: 103, 1961.
8. Pearse, A. G. E. Histochemistry, Theoretical and Applied, p. 154. Boston, 1960. Little Brown & Co.
9. Friedman, S. and Ash, R. Glycogen storage disease of the heart. Clinical observations in five infants. *J. Pediat.*, 52: 635, 1958.
10. Krivit, W., Polglase, W. J., Gunn, F. D. and Tyler, F. H. Studies in disorders of muscle. IX. Glycogen storage disease primarily affecting skeletal muscle and clinically resembling amyotonia congenita. *Pediatrics*, 12: 165, 1953.
11. Clement, D. H. and Godman, G. D. Glycogen disease resembling mongolism, cretinism, and amyotonia congenita. Case report and review of the literature. *J. Pediat.*, 36: 11, 1950.
12. Illingworth, B., Cori, G. T. and Cori, C. F. Amylo-1,6-glucosidase in muscle tissue in generalized glycogen storage disease. *J. Biol. Chem.*, 218: 123 1956.

Diagnostic Shelf

Concealed Retrograde Conduction*

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CONDUCTION through the atrioventricular node and the conducting system does not result in an electrocardiographic deflection but is inferred from the duration of the P-R interval. Occasionally, anterograde penetration of the A-V node is incomplete and thus is not followed by ventricular activation. Similarly, retrograde penetration of the A-V node may occur without subsequent activation of the atria. This phenomenon has been termed *concealed* conduction.† The degree of penetration cannot be measured directly but its presence is recognized by subsequent disturbance of conduction or impulse formation.

The following is an example of concealed retrograde conduction of a ventricular extrasystole permitting temporary A-V nodal rhythm with dissociation.

ANALYSIS OF ELECTROCARDIOGRAM

The electrocardiogram (Fig. 1) shows a basic rhythm in the first two complexes with a discharge rate of 0.74 second. This is followed by a ventricular extrasystole. The P wave of the third sinus impulse is dissociated from the ventricular extrasystole and may be seen superimposed upon the S-T segment of this extrasystole. The ventricular extrasystole is followed by three nodal beats occurring at a discharge rate of 0.79 second. The QRS complexes of the nodal beats are unrelated to the P waves of the sinus rhythm and this short period of nodal rhythm therefore occurs with A-V dissociation. Following this, sinus rhythm once again ensues.

This recording thus demonstrates that the sinus discharge rate is 0.74 second (illustrated as S1-S2 in Figure 2), and the potential nodal discharge rate is 0.79 second (illustrated as Nl-N2 in Figure 2). The nodal discharge does not normally become manifest because its impulse is prematurely discharged by the faster sinus rhythm. For example, the sinus impulse S1 in Figure 2 discharges the nodal pacemaker N1. This nodal pacemaker, if left undisturbed, would discharge 0.79 second later at point N2. However, its immature impulse is prematurely discharged at point X by the earlier sinus impulse (S2). Similarly, if the third sinus impulse (S3) had penetrated the A-V node and discharged the nodal pacemaker at position N3, the following sinus impulse (S4) would have occurred before the next nodal discharge (N4) and nodal rhythm would have been impossible. The fact that the nodal discharge did indeed occur earlier than the sinus discharge therefore indicates that the third sinus impulse (S3) did *not* discharge the nodal pacemaker at position N3. The nodal pacemaker was therefore discharged earlier and the only possible means for this discharge is retrograde conduction into the A-V node of the earlier impulse from the ventricular extrasystole (E in Figure 2). Thus, the nodal pacemaker is prematurely discharged at position Y instead of N3. This enables the succeeding nodal impulse to occur before it is reached by the sinus impulse i.e., at position Z instead of N4, and a nodal beat with dissociation occurs.

Dissociation persists for three beats with the fast sinus impulses occurring progressively earlier than the nodal impulses, until eventually a sinus impulse occurs sufficiently early to capture the ventricles and sinus rhythm once again ensues.

† LANGENDORF, R. and PICK, A. Concealed conduction. Further evaluation of a fundamental aspect of propagation of the cardiac impulse. *Circulation*, 13: 381, 1956.

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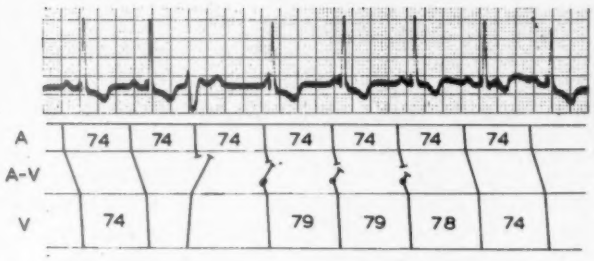

FIG. 1. Electrocardiogram, standard lead I. A = atrial level; A-V = A-V nodal level; V = ventricular level.

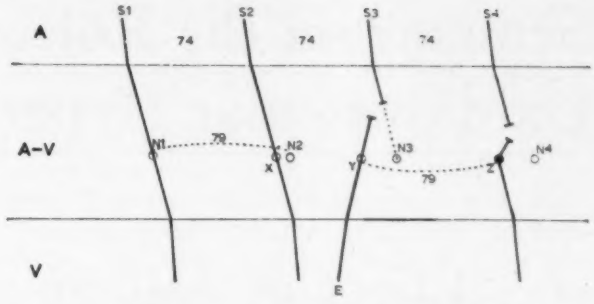

FIG. 2. Diagrammatic representation of the conduction abnormalities of the first four beats in Figure 1.

SUMMARY

A ventricular extrasystole is followed by temporary nodal rhythm with A-V dissociation. This is due to the retrograde penetration of the A-V node by the extrasystolic impulse which discharges the A-V nodal pacemaker prematurely. This enables the nodal escape to occur before the arrival of the next sinus impulse and nodal rhythm ensues. Retrograde conduction of the extrasystolic impulse is thus inferred from the subsequent disturbance of rhythm—*concealed conduction.*

ACKNOWLEDGMENT

I would like to express my thanks to the Photographic Unit, Department of Medicine, University of the Witwatersrand, for the photographic reproductions.

Seminar on the Role of Salt in Cardiovascular Hypertension (Part II)

Effect of Salt on the Kidney and the Juxtaglomerular Apparatus*

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ALL MAMMALS have a marvelous ability to retain a proper amount of sodium and extracellular fluid in the body. This regulatory mechanism is clearly demonstrated by the changes in the rate of sodium excretion stepwise with changes in the intake of sodium in the kidney. If, for instance, the sodium in the diet is abruptly changed from 1 per cent to 0.002 per cent, the sodium in the urine will progressively decrease over the next few days until it has almost disappeared from the urine after 6 or 7 days. At this point the mammal usually maintains sodium balance with a basic amount of body sodium, even with this low intake of sodium. When balance is achieved, the mammal is not unhealthily depleted of sodium, even though the intake and output are both very low. And as the amount of sodium decreases each day in the urine, the amount put out on a given day is proportional to the amount of sodium remaining in the body in excess of the basic level. With very high intakes of sodium and water *ad libitum*, the reverse of this phenomenon occurs. The kidneys excrete large amounts of sodium until a balance is achieved and the daily excretion matches the daily intake. This regulation is not absolutely perfect. Evidence indicates that both the blood volume and extracellular fluid volume are lower on a very restricted sodium intake than they are during a generous intake of salt. In various diseases associated with edema this mechanism stuffs the body with sodium, probably as an inappropriate response to an appropriate signal. During hemorrhage or dehydration or the pooling of blood associated with an upright posture, the mechanism acts to provide a conservation of sodium by the kidney.

ROLE OF JUXTAGLOMERULAR APPARATUS

Now the question concerns the mechanism by which the renal excretion of sodium is so nicely attuned to the effective volume of blood and extracellular fluid. In hemorrhage, venous pooling, dehydration, heart failure, cirrhosis, nephrosis and a low salt intake, all states where the excretion of sodium is very low, can we find a common denominator? One possible common denominator would be a diminished amount of blood in the arteries, causing them to be underdistended. Hence, we might profitably look for a stretch receptor in the wall of some arterial structure which would signal when the arteries are over- or underdistended. Bartter has found evidence for some type of volume receptor in the carotid artery. There may be a number of volume receptors in different parts of the circulation. I would like to consider the juxtaglomerular apparatus as an important volume-regulating system. This apparatus consists of the granular secretory juxtaglomerular cells which actually lie within the wall of the afferent glomerular arteriole and the adjacent macula densa cells which form a specialized plaque of cells in the wall of the distal convoluted tubule at its proximal end. The granular juxtaglomerular cells are in the wall of the afferent arteriole; therefore, they are in a perfect anatomic position to appreciate overdistention or underdistention of

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the arteriolar wall. There is evidence suggesting that these cells do react to changes in stretch. If a Goldblatt clip is placed on one renal artery, the juxtaglomerular granules practically double in the clipped kidney and virtually disappear in the contralateral untouched kidney.[1] If this untouched kidney is then clipped, the granules reappear in it.[1] If the clipped kidney is removed, thereby removing the hypertension, the granules reappear in normal abundance in the untouched kidney.[1] In various forms of experimental hypertension, whenever a kidney is exposed to elevated arterial pressure levels the number of juxtaglomerular granules in it become markedly reduced.[1]

Moreover, adrenalectomy increases the number of juxtaglomerular granules present,[1-3] while desoxycorticosterone plus salt causes them to disappear.[1,3] When desoxycorticosterone is given in conjunction with a very low intake of sodium, the number of granules decreases only slightly.[1] If a clip is placed on one renal artery so that the rat becomes severely hypertensive, the subsequent administration of desoxycorticosterone and salt to that rat will not diminish the juxtaglomerular granularity of the clipped kidney.[4]

If an isolated normal kidney is perfused at normal pressures for 3 hours, its juxtaglomerular granularity does not change. If the same type of kidney is perfused with high pressures (between 167 and 192 mm. Hg) the juxtaglomerular granularity becomes distinctly lower.[5]

All the foregoing observations would fit the hypothesis that when the renal arterial bed was overdistended with either high pressure or increased volume, the juxtaglomerular granules were reduced in number. Whenever the arterial system of the kidney was underdistended because of lower pressure or diminished volume, the granules of the juxtaglomerular cells increased.

Salt and the Juxtaglomerular Apparatus

For this seminar, the effect of salt itself is particularly pertinent. A diet very low in sodium causes a considerable increase in the juxtaglomerular granules.[1,3] It sometimes causes a hyperplasia of the juxtaglomerular cells. Conversely, a diet with 7.4 per cent NaCl causes a significant decrease in juxtaglomerular granularity.[6] These observations could readily fit in with our hypothesis. A low salt diet decreases blood volume slightly[7] which probably means that the volume of blood in the afferent arterioles is also decreased. This would underdistend the juxtaglomerular cells and they would become hypergranular. A high intake of sodium would increase blood volume and, therefore, probably increase the stretch of the juxtaglomerular cells and cause a degranulation. Since hypergranularity is associated with hyperplasia, it seems likely that an increase in granularity represents hypersecretion of these cells and a diminished granularity represents a low rate of secretion.

Renin and the Juxtaglomerular Apparatus

The next thing to consider is the relationship between renin and the juxtaglomerular cells. The available evidence indicates that virtually all the renin in a kidney is confined to the juxtaglomerular apparatus, either the granular cells or the macula densa or both. In brief, the evidence rests on three points. First, the granularity of the juxtaglomerular cells and the amount of extractable renin in the kidney of a rat are strongly correlated in every chronic experimental situation.[8,9] The result of the salt-feeding experiment shows this most strikingly.[6] When juxtaglomerular granules have practically disappeared from a kidney, there is no extractable renin in that kidney. When the juxtaglomerular granules are in extra abundance, extractable renin is also present in excess amounts. Second, both Cook and Pickering[10] and Bing[11] have done independent microdissection studies on the renal cortex; both have come to the conclusion that the renin is either in the granular juxtaglomerular cells or in the macula densa. Bing favors a location in the macula densa. Thirdly, Hartroft and Edelman made fluorescent antibodies to renin and flooded them over a frozen section of kidney from a sodium-deficient rabbit. Most of the fluorescence was localized in the cytoplasm of the granular juxtaglomerular cells.[12] Just as the juxtaglomerular granules can increase or decrease, the amount of extractable renin can also rise or fall with different physiologic states. The renin-juxtaglomerular cell system should properly be considered as a single entity. Renin, as well as the juxtaglomerular cell, is influenced by changes in salt intake. Pitcock, Hartroft and Newmark[9] showed that a low intake of sodium increases extractable renin in rats. Me and Gross[6,13] have shown that a high intake of salt decreases the content of extractable renin. Both of these changes could be mediated through an increase or decrease in blood volume with consequent greater or lesser

degrees of stretching of the granular juxtaglomerular cells.

Juxtaglomerular Cells, Sodium Excretion and Blood Pressure Control

Assuming that the juxtaglomerular cells do act as stretch receptors, what role might they play in the control of sodium excretion and in the regulation of blood pressure? One fairly well documented relationship has to do with the fact that either renin or angiotensin can stimulate the adrenal cortex to secrete aldosterone.[14–16] Moreover, an acute hemorrhage will stimulate an increased secretion of aldosterone in a hypophysectomized dog. But, if the kidneys have been removed from such a dog, the same quantity of blood lost will not cause an increased production of aldosterone.[17,18] It is obvious that some renal element is necessary for this signal. Renin and angiotensin both stimulate the adrenal; therefore, it may be that the juxtaglomerular cells are an integral part of the signaling system. If the juxtaglomerular apparatus could increase its output of renin in response to a low salt diet, this would stimulate an increase in aldosterone secretion which would promote reabsorption of sodium from the lumen of the distal convoluted tubule.

The juxtaglomerular cell might also receive the initial stimulus in certain types of renal hypertension. When the main renal artery is narrowed, there is a drop in pressure downstream from the constriction, although the renal blood flow does not necessarily become lower. The whole renal arterial tree is underdistended. This would decrease the stretch of the juxtaglomerular cells which are the only really specialized cells in any of the renal arterial walls. Similarly, encapsulation of the kidney compresses the renal parenchyma as a whole while compressing the afferent arteriole from outside. This would also decrease the stretch of the juxtaglomerular cells. With either type of stimulus, a decreased stretch of the juxtaglomerular cells would result. This would cause a hypersecretion which might inhibit the normal antihypertensive mechanism in the kidney. Such an inhibition would bring on hypertension.

Summary

The mammalian kidney normally adjusts very accurately the amount of sodium and extracellular fluid in the body. The regulation is probably accomplished through the use of volume receptors. The juxtaglomerular apparatus probably acts as such a volume receptor, changing its rate of secretion inversely with changes in the degree of distention of the afferent glomerular arterioles. Most of the renin in a kidney is confined to the juxtaglomerular apparatus. The physiologic functions of renin are also the physiologic functions of the juxtaglomerular apparatus; they should always be considered together. The juxtaglomerular apparatus seems to have an important influence on the regulation of body sodium. It may also be the site where the initial stimulus is registered in the hypertension caused by a narrowing of the renal artery as well as the hypertension caused by encapsulation of the kidney.

References

1. Tobian, L., Thompson, J., Twedt, R. and Janecek, J. The granulation of juxtaglomerular cells in renal hypertension, desoxycorticosterone and postdesoxycorticosterone hypertension, adrenal regeneration hypertension, and adrenal insufficiency. *J. Clin. Invest.* 37: 660, 1958.
2. Wiedman, M. L., Dunihue, F. W. and Robertson, W. V. B. Effect of sodium chloride intake and mineralocorticoid level on the granularity of juxtaglomerular cells. *J. Endocrinol.*, 17: 261, 1958.
3. Hartroft, P. M. and Hartroft, W. S. Studies on renal juxtaglomerular cells. I. Variations produced by sodium chloride and desoxycorticosterone acetate. *J. Exper. Med.* 97: 415, 1953.
4. Tobian, L., Janecek, J. and Tomboulian, A. Juxtaglomerular granulation in experimental hypertension. *Federation Proc.*, 17: 163, 1958.
5. Tobian, L., Tomboulian, A. and Janecek, J. The effect of high perfusion pressures on the granulation of juxtaglomerular cells in an isolated kidney. *J. Clin. Invest.*, 38: 605, 1959.
6. Tobian, L. Physiology of the juxtaglomerular cells. *Ann. Int. Med.*, 52: 395, 1960.
7. Murphy, R. J. F. The effect of "rice diet" on plasma volume and extracellular fluid space in hypertensive subjects. *J. Clin. Invest.*, 29: 912, 1950.
8. Tobian, L., Janecek, J. and Tomboulian, A. Correlation between granulation of juxtaglomerular cells and extractable renin in rats with experimental hypertension. *Proc. Soc. Exper. Biol. & Med.*, 100: 94, 1959.
9. Pitcock, J. A., Hartroft, P. M. and Newmark, L. N. Increased renal pressor activity (renin) in sodium deficient rats and correlation with juxtaglomerular granulation. *Proc. Soc. Exper. Biol. & Med.*, 100: 869, 1959.
10. Cook, W. F., and Pickering, G. W. The location of renin within the kidney. *J. Physiol.*, 143: 78, 1958.
11. Bing, J. and Kazimierczak, J. Renin content of different parts of the periglomerular circumference. *Acta path. et microbiol. Scandinav.*, 50: 1, 1960.

12. HARTROFT, P. M. and EDELMAN, R. Renal juxtaglomerular cells in sodium deficiency, localization of renin by the fluorescent antibody technique. In: Edema, Mechanisms and Management, p. 63. Edited by Moyer, J. H. Philadelphia, 1960. W. B. Saunders.
13. GROSS, F., LOUSTALOT, P. and SULSER, F. Die Bedeutung von Kochsalz fur den Cortexonhochruck der Ratte und den Gehalt der Nieren an pressorischen Substanzen. *Arch. f. exper. Path. u. Pharmakol.*, 229: 381, 1956.
14. DEANE, H. W. and MASSON, G. M. C. Adrenal cortical changes in rats with various types of experimental hypertension. *J. Clin. Endocrinol.*, 11: 193, 1951.
15. BIRON, P., KOIW, E., NOWACZYNSKI, W., BROUILLET, J. and GENEST, J. The effects of intravenous infusions of valine-5 angiotensin II and other pressor agents on urinary electrolytes and corticosteroids, including aldosterone. *J. Clin. Invest.*, 40: 338, 1961.
16. LARAGH, J. H., ANGERS, M., KELLY, W. G. and LIEBERMAN, S. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *J.A.M.A.*, 174: 96, 1960.
17. DAVIS, J. O., CARPENTER, C. J. C., AYERS, C. R., HOLMAN, J. E. and BAHN, R. C. Evidence for secretion of an aldosterone-stimulating hormone by the kidney. *J. Clin. Invest.*, 40: 684, 1961.
18. MULROW, P. J. and GANONG, W. F. The mechanism of aldosterone stimulation following hemorrhage in the hypophysectomized dog. *J. Clin. Invest.*, 40: 1065, 1961.

Effect of Sodium Chloride on the Thyroid Gland and on Iodide Metabolism*

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PROLONGED ADMINISTRATION of sodium chloride may affect considerably the function as well as the morphology of the thyroid gland.[1,2] An increase in the size of the gland may even occur if the animals are fed a diet with a critical or a low iodine content. Such a diet alone may, of course, induce a goiter (Fig. 1). This is the well-known iodine deficiency goiter which is well developed in the mouse after 2 months on the low iodine diet. When sodium chloride is added to the same diet, the mice have larger goiters (Fig. 1.). The extent of this effect depends on the level of salt in the diet and also on the level of iodine. In an experiment in which various levels of sodium chloride and iodine were used, it was found that at some levels of iodine concentration sodium chloride had no effect on the *weight* of the thyroid gland but did produce a stimulation of the gland which was readily recognizable histologically (Fig. 2). The amount of colloid was decreased and the cells were hypertrophied. The stimulation increased with the level of NaCl and was inversely related to the level of iodine in the diet. Adding 3 per cent sodium chloride to the diet led to approximately the same thyroid condition as lowering the iodine to NaCl level in the ratio 3:1 (Fig. 2).

MECHANISM OF SALT-INDUCED GOITER

Increased Urinary Excretion of Chloride: The mechanism by which thyroid stimulation and goiter are brought about by sodium chloride has been investigated in detail.[2] In two groups of mice fed the low iodine diet for a period of 2 months with or without added sodium chloride, salt about doubled the amount of iodide excreted into the urine (Fig. 3). This steady loss of iodide must have reduced the amount of iodine available to the thyroid gland because 2 months after the start of the experiment the iodine content of the thyroids in the animals ingesting salt was only a quarter of that of mice not eating sodium chloride (Fig. 4). It is probable that under these conditions the rate of secretion of thyroid hormone and the hormone level in blood were low. This probability was reflected by the small amount of thyroid hormone excreted in the feces, as measured by fecal iodine which is known to consist essentially of organic iodine[5] (Fig. 5).

The effect of sodium chloride on the metabolism of iodine could be demonstrated in a more dramatic fashion with the help of radioiodine.[2]

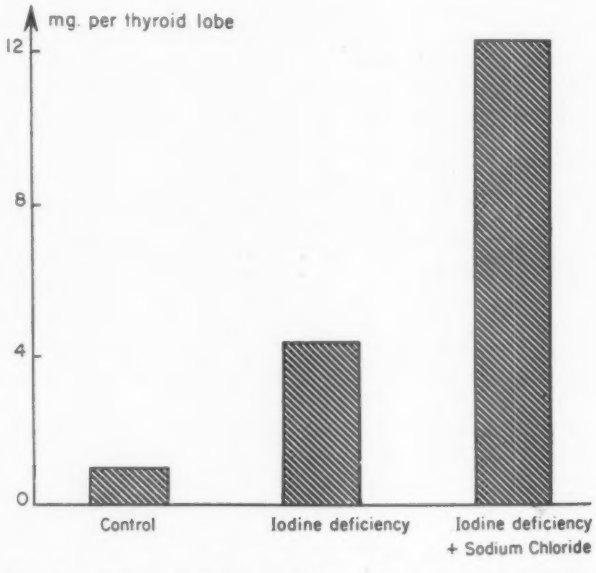

FIG. 1. Effect of dietary sodium chloride on the weight of the thyroid gland in mice fed a low iodine diet for a period of 2 months. While the low iodine diet with no salt added produced a four-fold increase, the same diet to which 1 per cent sodium chloride was added induced a twelve-fold increase over the weight of the thyroid observed in control mice with an adequate intake of iodine.

* From the Department of Biology, University of Montreal and Department of Anatomy, McGill University, Montreal, Canada.

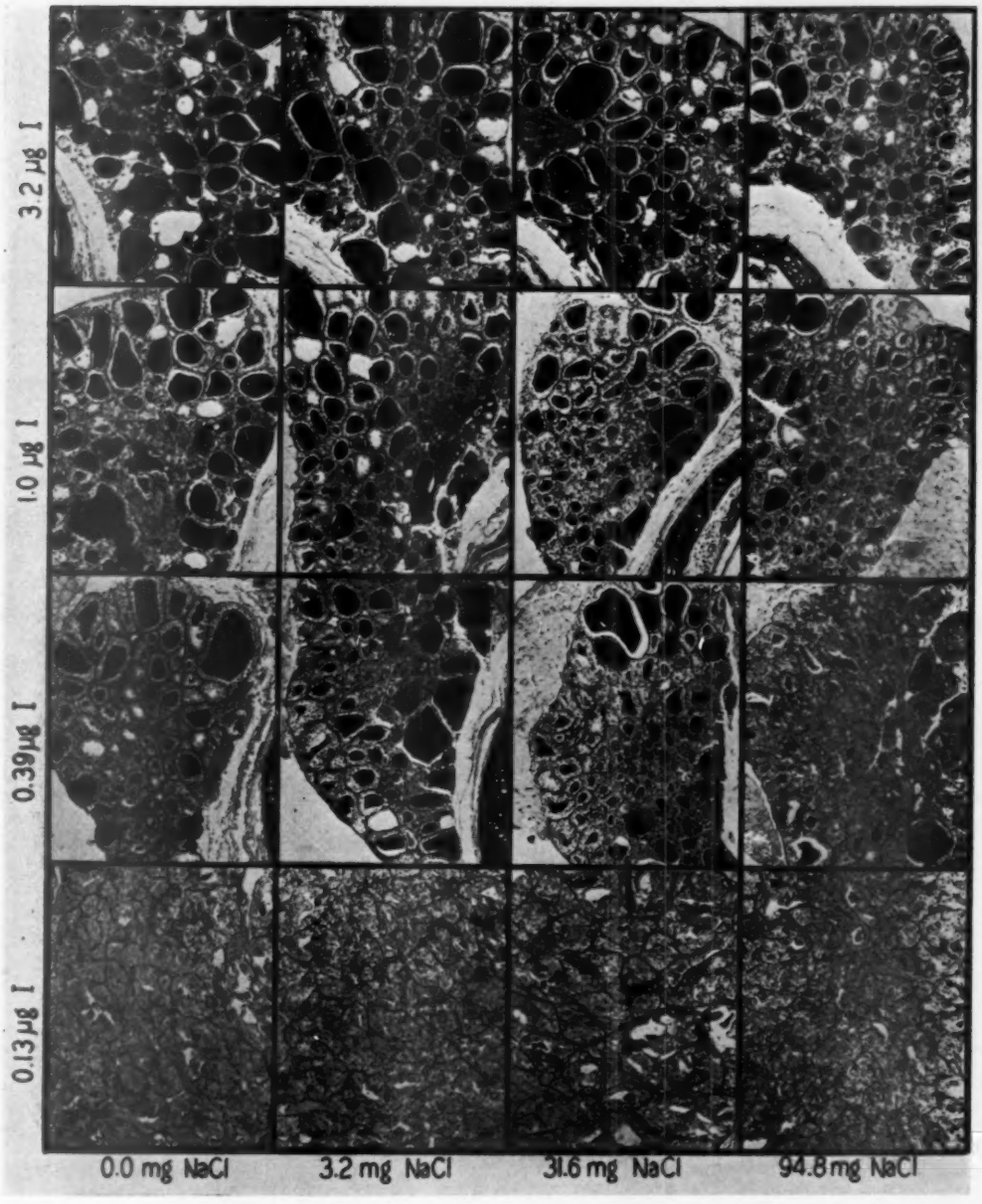

FIG. 2. Typical thyroid glands from mice with graded intakes of sodium chloride, as indicated on the bottom row (daily intake), and with graded intake of iodine as indicated in the left margin (daily intake). Thyroid stimulation increased as the sodium chloride intake rose and the iodine intake diminished.

Mice were injected with radioiodine and received an intragastric injection of 30 mg. sodium chloride immediately after. Three hours later they had excreted a considerable amount of radioiodine in their urine. In fact, the iodide losses were ten to twenty times larger than those in the animals not receiving salt (Fig. 6). Incidentally, the radioiodine content of the thyroid was not changed (Fig. 6). This indicates that whatever effect is produced by sodium chloride on the thyroid, this effect occurs after the initial increase in urinary excretion.

Reduced Iodide Content of Thyroid Gland: That the enormous urinary losses of iodide were actually depriving the thyroid of a large share of its normal iodide was apparent in animals sacrificed at longer time intervals. After 24 hours the radioiodine content of the thyroid was only a half that found in mice not receiving salt (Fig. 7). The level of radioiodine in the blood was also low (Fig. 7). The changes in urinary and blood radioiodide content could also be produced in thyroidectomized rats but not in nephrectomized mice (Table 1). This is taken

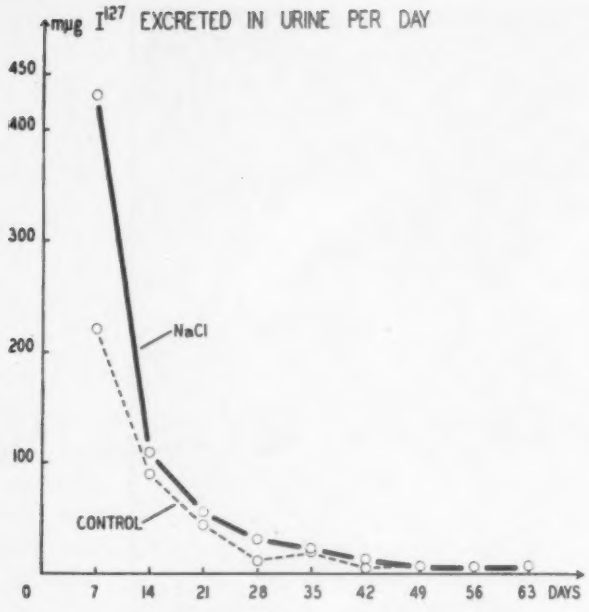

FIG. 3. Daily urinary iodide excretion in mice fed a low iodine diet for 63 days with either 1 per cent or no sodium chloride added to the diet. Salt induced a loss of iodide into the urine. FROM: Isler, H., Leblond, C. P. and Axelrod, A. A. *Endocrinology*, 62: 158, 1958.

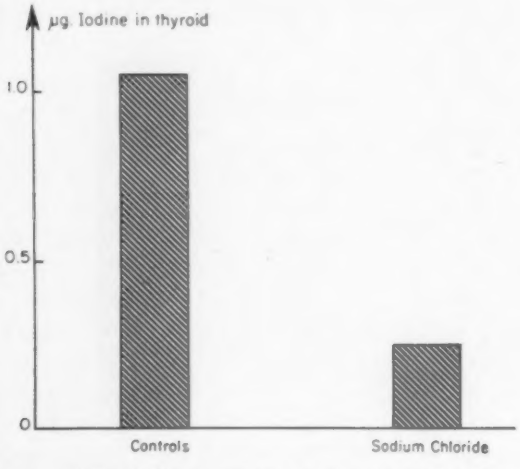

FIG. 4. Final iodine content in the thyroid gland of mice fed a low iodine diet for 63 days with either 1 per cent or no sodium chloride added to the diet. High intake of sodium chloride resulted in a low iodine content of the thyroid.

as further evidence that the urinary losses of iodide are the cause of the changes in iodide concentration in the blood and thyroid gland.

The large urinary excretion of iodide was due to a high clearance rate of this ion by the kidney. In fact, the blood clearance, as measured between the first and third hour following administration of 30 mg. sodium chloride, was increased from 0.007 to 0.152 ml. per minute, a factor of over twenty times (Fig. 8).

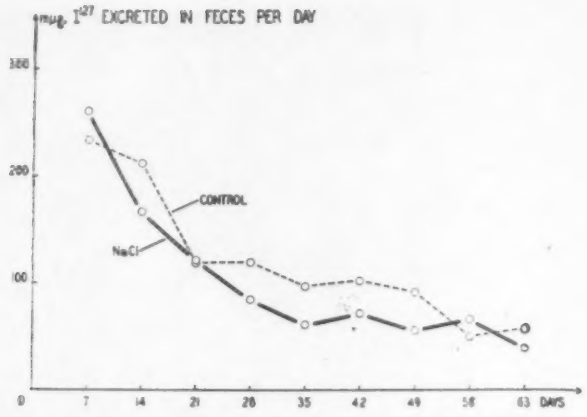

FIG. 5. Daily fecal excretion of iodine in mice fed a low iodine diet for 63 days with either 1 per cent or no sodium chloride added to the diet. Mice on a high salt intake excreted less fecal iodine. FROM: Isler, H., Leblond, C. P. and Axelrod, A. A. *Endocrinology*, 62: 158, 1958.

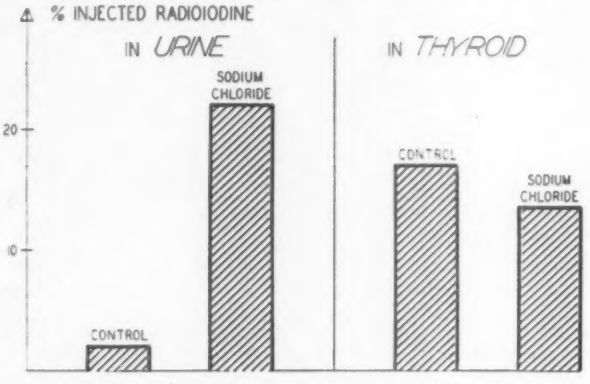

FIG. 6. Effect of sodium chloride on the urinary excretion and thyroid uptake of radioiodine as measured 3 hours after simultaneous injection of radioiodine (subcutaneous) and 30 mg. sodium chloride (intragastric). Salt considerably increased the urinary losses of radioiodine.

Change in Iodide Distribution: Thus, sodium chloride induced a change in the final distribution of iodide in the body. This ion is continuously displaced from one part of the body to another, but *ultimately* its fate is either to be eliminated in the urine or enter the thyroid gland to be incorporated into organic molecules. Under normal conditions, about 60 per cent of the total amount of iodide administered was eliminated in the urine and 40 per cent was organified in the thyroid gland. Injection of 30 mg. sodium chloride drastically changed this distribution since only 4 per cent reached the thyroid while 96 per cent was lost in the urine (Fig. 9). When the thyroid pump was more efficient, as in mice fed a low iodine diet, the thyroid gland of control mice took up 81 per cent, leaving only 19 per cent to the urine. An injec-

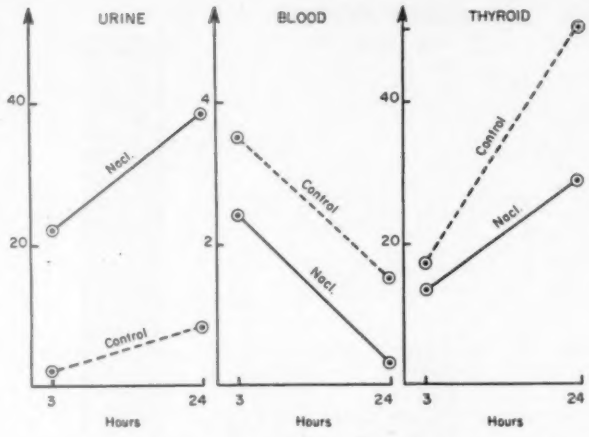

FIG. 7. Effect of sodium chloride on the urinary excretion, blood level and thyroid uptake of radioiodine as measured 3 and 24 hours following simultaneous injection of radioiodine (subcutaneous) and 30 mg. sodium chloride (intragastric). The vertical scale indicates the per cent of injected radioiodine. Administration of salt first caused heavy urinary losses (at 3 hours) and later (at 24 hours) resulted in a low blood level and thyroid content of radioiodine.

TABLE I

Effect of Sodium Chloride on Radioiodine Metabolism in Thyroidectomized and Nephrectomized Mice as Measured 2.5 Hours after Intragastric Injection of 30 mg. Sodium Chloride

Mice	Sodium Chloride (mg.)	Radioiodine*		
		Thyroid	Blood (1 ml.)	Urine
Control	0	10.6	4.3	0.5
	30	10.5	1.9	11.8
Nephrectomized	0	10.8	5.3	...
	30	11.4	5.3	...
		(Trachea)		
Thyroidectomized	0	0.13	10.4	1.1
	30	0.07	7.3	11.1

NOTE: Underlined values are significantly different from those of animals not receiving sodium chloride.

* Expressed in per cent of injected dose.

FROM: Isler, H., Leblond, C. P. and Axelrod, A. A. *Endocrinology*, 62: 159, 1958.

tion of sodium chloride to these animals reversed the distribution and induced a 74 per cent loss in the urine, allowing only 26 per cent to be taken up by the thyroid gland (Fig. 9).

EFFECT OF OTHER IONS AND HORMONES

Effect of Various Salts: An investigation was also carried out to determine whether

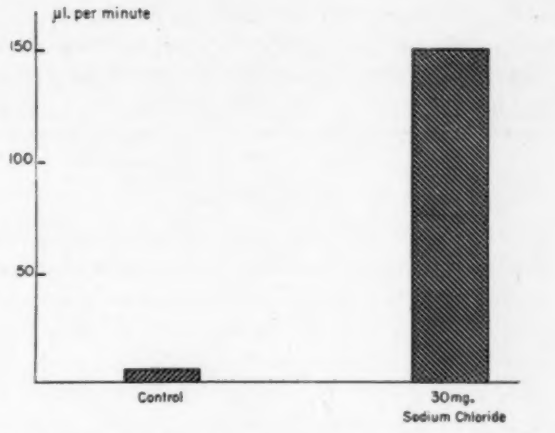

FIG. 8. Effect of a single intragastric injection of sodium chloride on the blood radioiodine clearance by the kidney as measured between the first and third hour following administration of 30 mg. salt. The clearance underwent a twenty-fold increase.

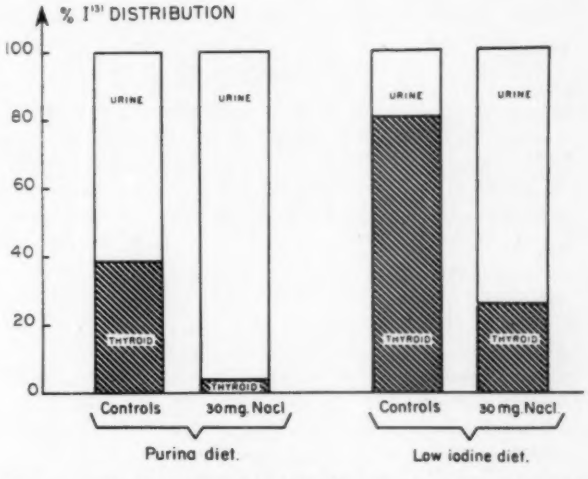

FIG. 9. Distribution of radioiodine between the thyroid gland and the urine in mice with an adequate and a low iodine intake. In both cases, a single intragastric injection of 30 mg. sodium chloride considerably reduced the amount of radioiodine in the thyroid gland.

the effect of sodium chloride on iodide metabolism was due to the presence of sodium ions, chloride ions or both, and whether other ions or salts could also affect the excretion of iodide.[3] When various salts were introduced into the stomach of mice previously injected with radioiodine, it was found that either sodium or chloride ions alone could produce the effect, as well as other halides or alkalies (Table II). However, not all salts were effective; those such as lithium, ammonium, calcium, carbonate and acetate ions which were poorly ionized or likely to be precipitated into insoluble compounds in the body fluid were not; uncharged molecules

TABLE II

Acute Effect of 0.517 mEq. of Various Salts on the Urinary Excretion and Thyroid Uptake of Radioiodine in Mice

Treatment	No. Mice	Radioiodine*	
		Urine (Mean ± S.E.)	Thyroid (Mean ± S.E.)
Control	8	3.7 ± 1.2	23.1 ± 2.8
Lithium carbonate (Li_2CO_3)	7	5.5 ± 1.6	7.9 ± 4.5
Control	8	9.9 ± 2.3	12.7 ± 1.6
Lithium acetate	7	13.7 ± 5.5	9.1 ± 1.0
Control	6	4.7 ± 1.1	26.8 ± 3.1
Sodium bicarbonate ($NaHCO_3$)	7	37.2 ± 4.6	23.4 ± 2.9
Disodium phosphate (Na_2HPO_4)	7	33.6 ± 4.9	19.7 ± 1.2
Sodium chloride	7	53.8 ± 5.6	17.1 ± 1.4
Control	8	3.2 ± 0.9	23.4 ± 1.7
Potassium bicarbonate ($KHCO_3$)	3	30.9 ± 15.2	10.8 ± 2.6
Sodium chloride	8	56.2 ± 2.8	13.5 ± 1.2
Control	8	12.7 ± 3.1	11.8 ± 0.7
Rubidium carbonate (Rb_2CO_3)	8	38.9 ± 2.6	11.0 ± 2.0
Sodium chloride	8	47.8 ± 3.8	10.4 ± 1.2
Control	8	9.9 ± 2.3	12.7 ± 1.6
Ammonium carbonate $(NH_3)_2CO_2$	3	16.0 ± 5.0	13.1 ± 4.2
Sodium chloride	7	50.2 ± 5.3	14.4 ± 2.3
Control	8	3.2 ± 0.9	23.4 ± 1.7
Calcium acetate	7	1.1 ± 0.3	9.7 ± 1.5
Acetic acid	8	0.4 ± 0.1	7.5 ± 1.5
Control	8	3.1 ± 0.6	10.4 ± 3.6
Lithium fluoride	7	6.9 ± 2.4	11.4 ± 5.3
Lithium chloride	7	14.1 ± 2.5	12.3 ± 4.4
Lithium bromide	8	17.3 ± 2.4	11.0 ± 4.6
Lithium iodide	8	38.5 ± 5.0	0.14 ± 0.04
Sodium chloride	8	55.6 ± 2.8	7.1 ± 3.2
Glucose	8	3.4 ± 1.0	8.5 ± 2.3
Water (0.1 ml.)	8	3.1 ± 0.7	15.3 ± 2.7
Water (1.5 ml.)	8	2.7 ± 1.0	15.7 ± 1.3

NOTE: The underlined values are significantly different from the respective control subjects.

* Expressed as per cent of injected dose.

FROM: Isler, H. *Endocrinology*, 64: 769, 1959.

such as glucose and water were not either (Table II). Only those substances which are likely to cause the ionic concentration of blood to rise enhanced the excretion of radioiodide.

Adrenal and Pituitary Hormones: The urinary excretion of iodide was influenced very little by the hormones of the adrenal glands such as cortisone, desoxycorticosterone, aldosterone, epinephrine and norepinephrine, or by hormones of the anterior pituitary.[4] However, excretion of iodide was strongly enhanced by the hormones of the posterior pituitary: vasopressin and oxytocin[4] (Fig. 10). The amount of radioiodine excreted varied linearly with the logarithm of the dose of hormone. Like sodium chloride, vasopressin enhanced the blood clearance of the iodide ion (Fig. 11).

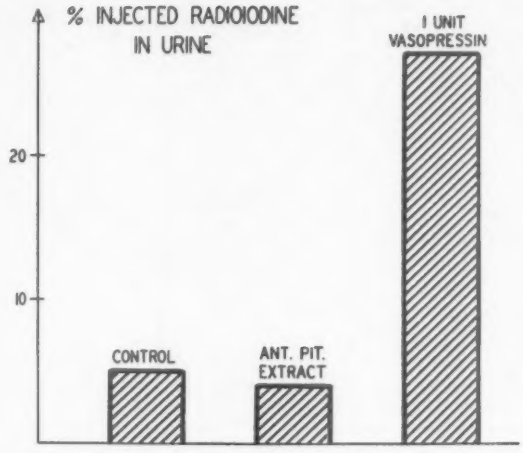

FIG. 10. Effect of anterior and posterior pituitary on the urinary excretion of radioiodine as measured 2.5 hours after subcutaneous injection of pituitary preparations. Vasopressin strongly enhanced iodide losses in the urine.

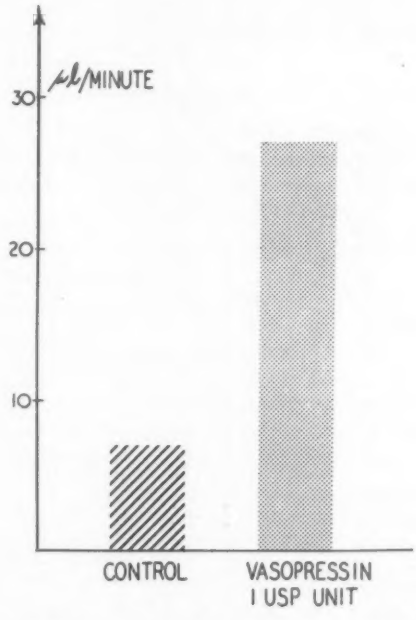

FIG. 11. Effect of vasopressin on blood radioiodine clearance by the kidney as measured between the first and third hour following injection of 1 U.S.P. unit of hormone.

Experiments by Leveque[6] had shown that sodium chloride induces a release of the vasopressin-containing neurosecretory material in the hypothalamus; therefore there was a possibility that the effect of sodium chloride on

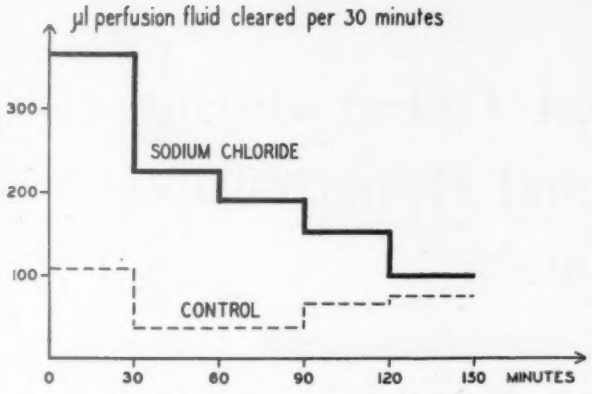

FIG. 12. Effect of sodium chloride on the radioiodine clearance by the isolated rabbit kidney. The clearance was enhanced by salt.

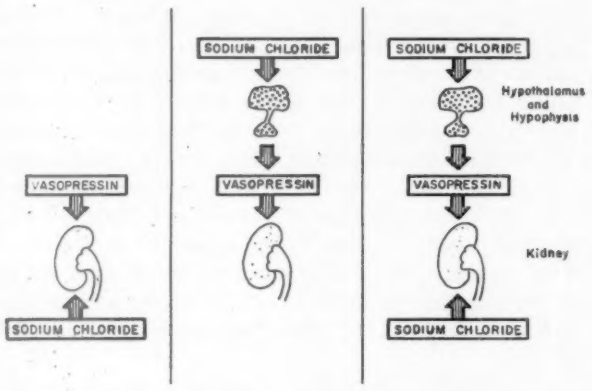

FIG. 13. Three hypotheses accounting for the high urinary excretion of radioiodine observed after sodium chloride administration. The second possibility was excluded by the observation that the high excretion occurs also in the isolated kidney.

iodide excretion was mediated by posterior pituitary hormones. That is, sodium chloride might cause the release of vasopressin into the circulation, which in turn would enhance clearance of iodide from the blood by the kidney.

This hypothesis was investigated in the isolated kidney. Isolated kidneys of rabbits were perfused with radioiodine-containing fluids with or without added sodium chloride. This salt did actually increase the iodide clearance of the isolated kidney (Fig. 12). This indicates that, although an effect through the posterior pituitary hormones is not excluded, sodium chloride has a direct effect of its own on the kidney, sufficient to account for the large excretion of iodide observed in our mice (Fig. 13).

CONCLUSIONS

Sodium chloride modifies the clearance of iodide from the blood by the kidney, thus causing enormous losses of this ion into the urine. These losses restrict the uptake of iodine by the thyroid gland and consequently diminish the rate of synthesis and of secretion of thyroid hormone. The pituitary gland responds to the low level of this hormone in the blood by releasing thyrotropic hormone which in turn stimulates the thyroid gland. Under condition of critical iodine intake the urinary losses induce a condition of iodine deficiency which results in a persisting stimulation of the thyroid and, eventually, in goiter.

ACKNOWLEDGMENT

The collaboration of C. P. Leblond, A. A. Axelrod and R. Blake at some phases of this work is acknowledged. This project was supported by a grant from the Department of National Health and Welfare of Canada (obtained through the Ministry of Health of the Province of Quebec).

REFERENCES

1. AXELROD, A. A., LEBLOND, C. P. and ISLER, H. Role of iodine deficiency in the production of goiter by the Remington diet. *Endocrinology*, 56: 387, 1955.
2. ISLER, H., LEBLOND, C. P. and AXELROD, A. A. Mechanism of the thyroid stimulation produced by sodium chloride in the mouse. *Endocrinology*, 62: 159, 1958.
3. ISLER, H. The acute effect of salts on the urinary excretion of radioiodide in mice. *Endocrinology*, 64: 769, 1959.
4. ISLER, H. The effect of adrenal and pituitary hormones on the urinary excretion of iodide in mice. *Endocrinology*, 64: 807, 1959.
5. GROSS, J. and LEBLOND, C. P. Metabolites of thyroxine. *Proc. Soc. Exper. Biol. & Med.*, 76: 686, 1951.
6. LEVEQUE, T. F. Changes in neurosecretory cells of the rat hypothalamus following ingestion of sodium chloride. *Anat. Rec.*, 117: 741, 1953.

Activity of Thyroid Gland during Development of Renal Hypertension in Rats*

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STUDIES CONDUCTED in this laboratory and elsewhere during the past few years have implicated the thyroid gland as a possible etiologic factor in the development of experimental hypertension. Treatments that prevent or greatly reduce the activity of the thyroid gland also prevent the development of both renal and NaCl-induced hypertension.[1–3] The present studies were conducted to determine the functional status of the thyroid gland during development of renal hypertension. The results suggest that the thyroid gland plays an important secondary role in development of renal hypertension in the rat.

METHODS

Forty-nine male Holtzman rats were used. Thirty-nine had both kidneys encapsulated with latex envelopes,[4] the remaining rats served as nonencapsulated control subjects. The rats were kept two or three per cage in a thermoregulated room maintained at 26±1°C. and illuminated from 8 A.M. to 6 P.M. All rats were given ground Purina laboratory chow to eat and tap water to drink. Food containers were of the type described earlier;[5] fluid containers were similar to those described by Lazarow.[6] Blood pressures of the rats were measured by the microphonic manometer technic[7] but without anesthesia. Oxygen consumption was measured by the open circuit technic of Adolph[8] with the surrounding water bath maintained at a temperature of 27±0.5°C.

Rats were killed at 1, 2, 3, 4, 6, 11, 16 and 33 weeks after encapsulation of kidneys. Generally, five kidney-encapsulated and two control rats were killed at a time. The exceptions to this statement are that control rats were not killed during weeks 1, 3 and 16. Blood pressure, body weight and total body oxygen consumption of each rat were measured prior to sacrifice. In addition, each rat was injected intraperitoneally with 2 μc. of carrier-free radioactive iodide (NaI^{131}) 48 hours prior to death. Upon injection of radioactive iodide, each rat was placed in a metabolism cage for collection of urine under light mineral oil. Exactly 24 hours after injection, urine was collected, volume measured and a 1 ml. aliquot removed and radioactivity counted using a well-type scintillation detector. The radioactivity was corrected for physical decay of the isotope. Thus, total urinary output of radioactive iodide could be determined during this period.

Forty-eight hours after injection of radioactive iodide all rats were killed by guillotine decapitation. Blood was collected in chemically clean beakers for analysis of serum precipitatable I^{131}. For this purpose, 1 ml. of serum was added to 3 ml. of 10 per cent trichloroacetic acid and the filtrate washed twice with 3 ml. of trichloroacetic acid. The precipitate was dried and counted using a well-type scintillation detector. The radioactivity of an equal volume of serum was also counted. These activities were corrected for physical decay of the isotope. From these values the precipitate to serum activity (conversion) ratio was calculated for each rat. This ratio is used as a quantitative method for assessing level of circulating thyroid hormone.[9]

At sacrifice, the thyroid gland and heart of each rat were removed and weighed on a torsion balance. The thyroid gland was fixed in formalin and prepared for histologic examination by staining with hematoxylin and eosin. Thyroid acinar cell heights were counted from sections of each thyroid gland using a microscope (high, dry) with calibrated eyepiece. Sixty counts on at least five separate thyroid sections were made. The mean of these counts was considered to be the mean thyroid acinar cell height for that rat.

* From the Department of Physiology, University of Florida, College of Medicine, Gainesville, Florida. Supported by a grant from the American Heart Association and by Grant H-3503 from the National Heart Institute, National Institutes of Health, Bethesda, Maryland.

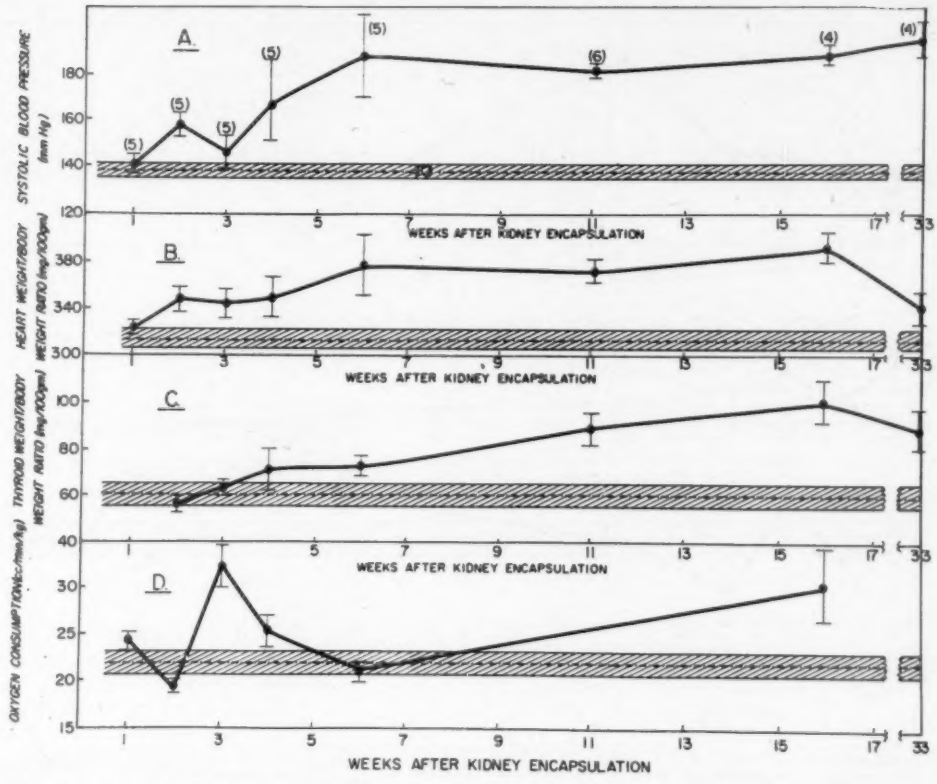

FIG. 1. A, systolic blood pressure of kidney-encapsulated rats during the course of the experiment. ±1 standard error is set off at each mean. Numbers in parentheses represent number of rats. Horizontal line represents mean and standard error of nonencapsulated control rats. B, heart weight to body weight ratio; C, thyroid weight to body weight ratio; and D, oxygen consumption during the course of the experiment.

RESULTS

Some results of this experiment are shown in Figure 1. The rise of systolic blood pressure with time is shown in Part A. Mean systolic blood pressure of the ten control, nonencapsulated rats is shown as the horizontal line at the bottom of the figure. Blood pressures became elevated within 2 weeks but reached maximal levels at 6 weeks after kidney encapsulation. This high level was maintained throughout the remainder of the experiment. In Part B the ratio of heart weight to body weight (mg. per 100 gm.) is shown. Heart weight ratio increased significantly within 2 weeks after kidney encapsulation. This ratio became maximal at 6 weeks but dropped to near-normal levels at 33 weeks. In Part C the ratio of thyroid weight to body weight (mg. per 100 gm.) is shown. By error, thyroid glands of the rats killed during the first week after kidney encapsulation were not weighed. A rise in thyroid weight ratio is observable during the fourth week after kidney encapsulation and is significantly different from control levels during the eleventh week. Thyroid weight ratio remained significantly elevated thereafter. In Part D oxygen consumption (cc. per minute per kg.) is shown. A slight elevation in oxygen consumption occurred during the first experimental week, followed by a decrease below control levels during the second. Oxygen consumption levels higher than control were observed during weeks 3, 4 and 16. During week 6, oxygen consumption level had returned within the control range.

Serum Conversion Ratio and I^{131} Excretion: In Figure 2, Part A, mean thyroid acinar cell height is shown. A significant increase in cell height was observed only during week 6. Mean values for other weeks were within the range of control rats. In Part B the serum precipitable I^{131} (per cent of injected dose) is shown. Values for experimental rats were higher than control values initially but returned to control level gradually. By the sixteenth week the value was identical with that of control rats. The conversion ratio (Part C) gave a triphasic response in which the values during

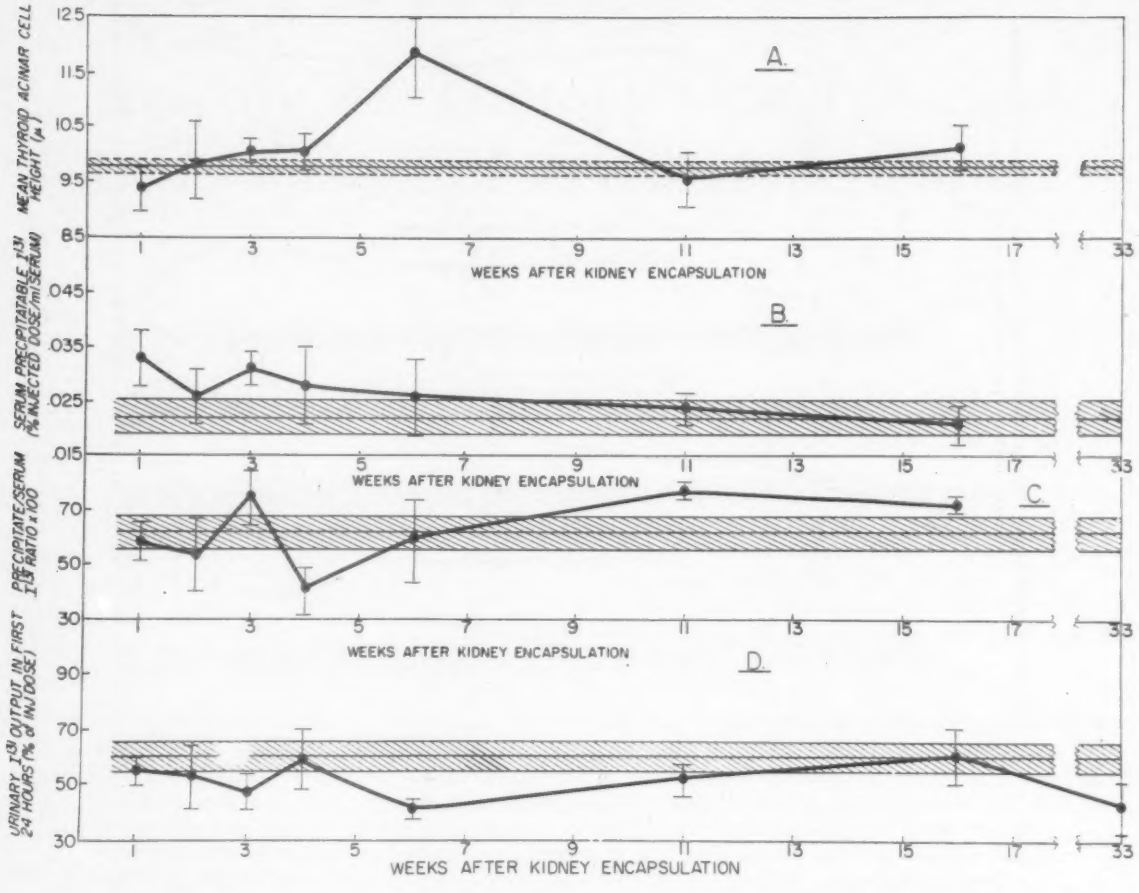
MEAN THYROID ACINAR CELL HEIGHT (μ)
A.
WEEKS AFTER KIDNEY ENCAPSULATION
SERUM PRECIPITATABLE I131 (% INJECTED DOSE/ml SERUM)
B.
WEEKS AFTER KIDNEY ENCAPSULATION
PRECIPITATE/SERUM I131 RATIO x 100
C.
WEEKS AFTER KIDNEY ENCAPSULATION
URINARY I131 OUTPUT IN FIRST 24 HOURS (% of INJ DOSE)
D.
WEEKS AFTER KIDNEY ENCAPSULATION

FIG. 2. A, mean thyroid acinar cell height of kidney encapsulated rats during course of the experiment. ±1 standard error is set off at each mean. B, serum precipitable I^{131}; C, precipitate/serum I^{131} ratio; and D, urinary I^{131} output in first 24 hours after injection are shown during course of experiment.

weeks 2 and 4 were lower than that of controls. During weeks 11 and 16, values rose to levels higher than control. Part D indicates that the control rats excreted on the average 60 per cent of the injected dose of I^{131} in urine within 24 hours after injection. Hypertensive rats usually excreted slightly less than this amount.

Heart Weight and Thyroid Weight Ratios: Figure 3, Part A, shows that without regard to time kidneys were encapsulated the relationship between heart weight ratio and systolic blood pressure is approximately sigmoid. As blood pressure increases to levels of 150 to 159 mm. Hg, heart weight ratio increases sharply. In Part B the relationship between thyroid weight ratio and systolic blood pressure is shown also without regard to time after kidneys were encapsulated. Thyroid weight remained relatively constant until blood pressure levels of 150 to 159 mm. Hg were reached. At pressures exceeding this level, thyroid weight ratio rose linearly with rising blood pressure. Part C shows that the relationship between thyroid weight ratio and heart weight ratio *at the same systolic blood pressures* is exponential. Thyroid weight ratio is little influenced by increasing heart weight ratio until the latter exceeds 335 mg. per 100 gm. body weight. Thyroid weight ratio then increases rapidly for small changes in heart weight ratio. Thus, it appears that as systolic blood pressure exceeds 149 mm. Hg, heart ratio increases sharply. However, thyroid weight ratio remains constant until blood pressure level exceeds 159 mm. Hg and heart weight ratio exceeds 335 mg. per 100 gm. body weight. When these threshold values are reached, thyroid weight ratio increases. Whether thyroid weight ratio increases in response to rising systolic pressure as the primary factor or to increasing heart weight ratio as the primary factor cannot be stated with certainty. However, the likelihood is that the thyroid gland responds primarily to the increased systolic pressure. It is worth noting that the threshold

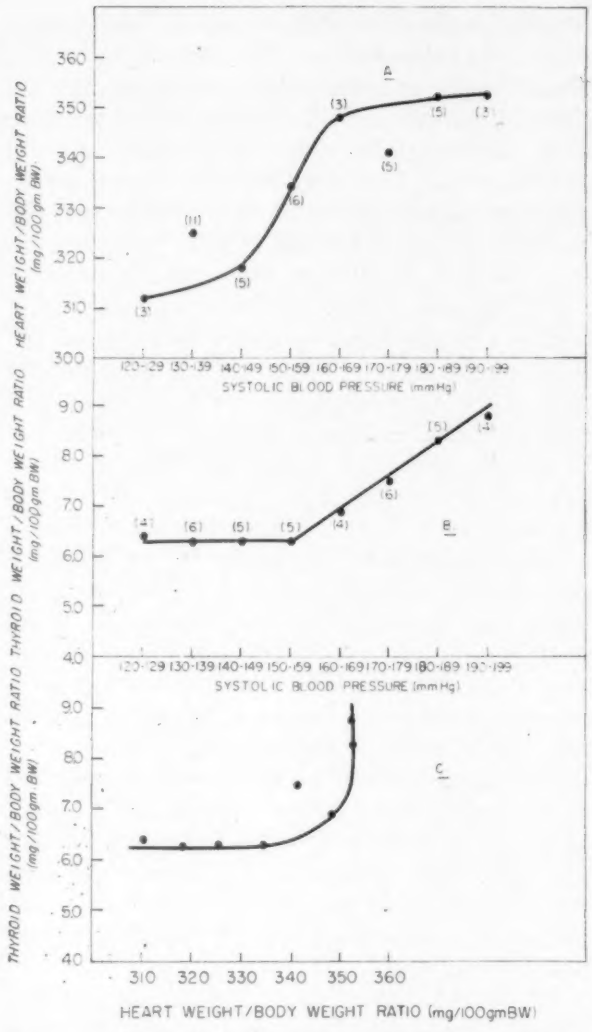
A
B
C
SYSTOLIC BLOOD PRESSURE (mmHg)
120-29 130-139 140-149 150-159 160-169 170-179 180-189 190-199
THYROID WEIGHT/BODY WEIGHT RATIO (mg/100gm BW)
HEART WEIGHT/BODY WEIGHT RATIO (mg/100gm BW)
310 320 330 340 350 360
HEART WEIGHT/BODY WEIGHT RATIO (mg/100gmBW)

FIG. 3. A, heart weight to body weight ratio of all rats, kidney-encapsulated and control, plotted against arbitrary ranges of systolic blood pressure without regard to time kidneys were encapsulated. Numbers in parentheses represent number of rats. B, thyroid weight to body weight ratio of all rats plotted against arbitrary ranges of systolic blood pressure as in (A). C, relationship between heart weight ratio and thyroid weight ratio at the same systolic blood pressure levels. Figure is redrawn from the data in (A) and (B).

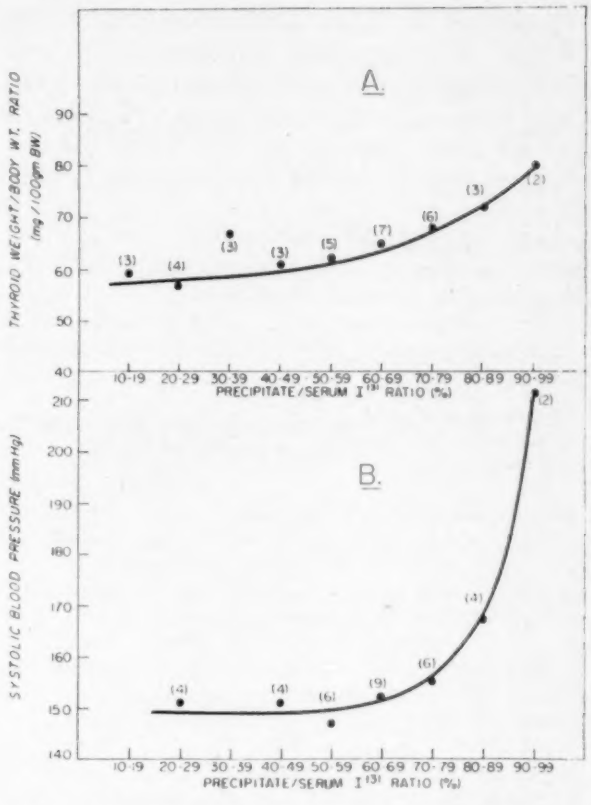
A.
B.
THYROID WEIGHT/BODY WT. RATIO (mg/100gm BW)
SYSTOLIC BLOOD PRESSURE (mmHg)
10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99
PRECIPITATE/SERUM I131 RATIO (%)

FIG. 4. Thyroid weight ratio (A) and systolic blood pressure (B) are plotted against arbitrary ranges of precipitate/serum I^{131} ratio without regard to time kidneys were encapsulated. Numbers in parentheses represent number of rats.

blood pressure level for increasing both heart and thyroid weight ratio is the level usually considered borderline between normotension and hypertension.

Serum I^{131} Thyroid Weight and Blood Pressure: In Figure 4 is shown the results of a plot in which precipitate to serum I^{131} ratio is considered the independent variable and thyroid weight ratio (Part A) and systolic blood pressure (Part B) the dependent variables. The latter are given for each arbitrary range of precipitate to serum I^{131} ratio. In Part A, a rise in precipitate to serum I^{131} ratio is accompanied by an increase in thyroid to body weight ratio. For a 100 per cent increase in precipitate to serum I^{131} ratio (from the range 40 to 49 to 90 to 99) a 30 per cent increase in thyroid weight ratio is observed. In Part B, an exponential rise in systolic pressure occurs as precipitate to serum I^{131} ratio increases. The threshold ratio appears to range between 60 to 69 and 70 to 79. For small increases in precipitate to serum I^{131} ratio beyond these levels, large increases in blood pressure occur.

Figure 5A indicates that the mean thyroid acinar cell height increases when a threshold value of systolic blood pressure in the range of 150 to 159 mm. Hg is reached. Similar threshold relationships exist between systolic blood pressure as the independent variable and either heart weight ratio (Fig. 3A) or thyroid weight ratio (Fig. 3B) as dependent variables. Oxygen consumption did not appear to bear a close relationship to systolic blood pressure and is not shown but it may be related to precipitate to serum I^{131} ratio in the fashion shown in Figure 5B. Again, a threshold-type response is sug-

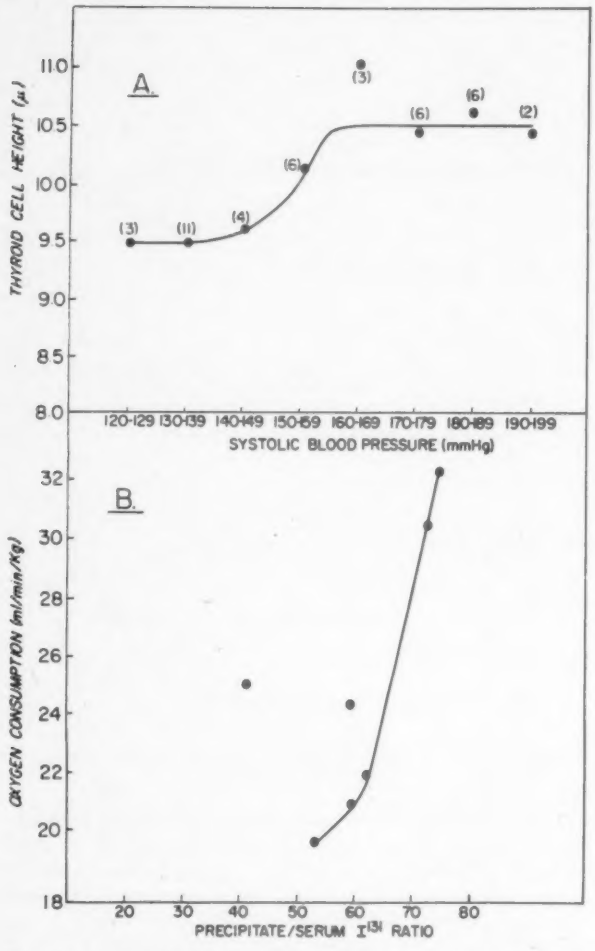

FIG. 5. A, thyroid cell height is plotted against arbitrary ranges of systolic blood pressure without regard to time kidneys were encapsulated. Numbers in parentheses represent number of rats. Cell height bears a clear relationship to systolic blood pressure. B, mean oxygen consumption graphed against mean precipitate to serum I^{131} ratio. The points compare the simultaneous means of these two measurements for weeks 1, 2, 3, 4, 6 and 16.

gested. This relationship is not entirely satisfactory because of the two points which lie to the left of the line. It is unfortunate that oxygen consumption was not measured on all rats in this experiment. This fact, coupled with the large variability associated with measurement of oxygen consumption in the rat, limits the usefulness of the relationship suggested in Figure 5B.

COMMENTS

These experimental results suggest that the thyroid gland may play an important secondary role in the development of renal hypertension in the rat. Thyroid activity, as assessed by thyroid weight to body weight ratio, precipitate to serum I^{131} ratio, and mean thyroid acinar cell height, increases sharply as systolic blood pressure level approaches 150 to 160 mm. Hg. Heart weight to body weight ratio increases in a sigmoid fashion with increasing blood pressure and exponentially with increasing thyroid weight ratio. One may visualize that a mechanism(s) independent of the activity of the thyroid gland increases blood pressure to levels of 150 to 160 mm. Hg. At this pressure level, thyroid gland activity increases and further elevates blood pressure to levels of 180 mm. Hg or more. Thus, kidney-encapsulated rats whose thyroid glands were removed just prior to encapsulation of the kidney showed rises in systolic blood pressure from initial levels of approximately 130 mm. Hg to levels of approximately 155 mm. Hg during the course of an experiment described earlier.[10] In this same experiment, blood pressures of kidney-encapsulated rats treated with the antithyroid drug, propylthiouracil, responded in the same fashion as the thyroidectomized rats while blood pressures of untreated, kidney-encapsulated control rats rose to levels of 180 mm. Hg. When antithyroid drugs were given to rats with established hypertension in another experiment,[11] blood pressures generally fell to levels of approximately 150 mm. Hg. These results support the idea that the effect of the thyroid gland on blood pressure is superimposed on another, more basic mechanism.

While this experiment fails to suggest the primary mechanism involved in the elevation of blood pressure, it does suggest a hitherto unsuspected secondary role for the thyroid gland in the development and maintenance of renal hypertension in the rat. The mechanism by which the thyroid gland is called into play cannot involve excess loss of iodide in urine with subsequent lowering of plasma iodide concentration and increased secretion of thyroid stimulating hormone. It was observed experimentally that renal excretion of radioactive iodide by kidney-encapsulated rats was never greater than that of nonencapsulated control rats and was generally less (Fig. 2D). It is recognized, however, that fecal loss of iodide must be taken into consideration before one can estimate and compare total iodide losses of kidney-encapsulated with control rats. Hence, it remains to be tested whether increased loss of iodide from the intestine could serve as a mechanism stimulating thyroid activity.

The mechanism by which increased thyroid activity maintains hypertension has not been

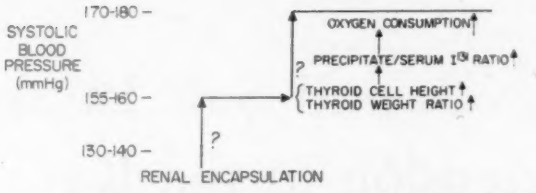

FIG. 6. A schema suggesting a secondary role for the thyroid gland in development of renal hypertension.

elucidated by these experiments. A possibility exists that the increase in thyroid activity increases vascular reactivity to circulating pressor agents. Brewster et al.[12] have observed that hyperthyroidism increases the sensitivity of the heart and blood vessels of dogs to infusions of catecholamines. The opposite reaction, i.e., decreased vascular reactivity to injected catecholamines in hypothyroidism, has been observed by McCubbin and Page[13] for dogs and Smith[14] for isolated swine aortas. A possibility also exists that cardiac output may increase with increase in thyroid activity and needs to be evaluated.

Until further evidence can be brought to bear, the schema shown in Figure 6 may be considered a tentative summary of the present experiments. Renal encapsulation elevates systolic blood pressure from control levels near 130 mm. Hg to levels near 160 mm. Hg by an unknown mechanism. At the latter pressure level, thyroid gland activity increases, as assessed by increases in thyroid cell height, thyroid weight ratio, precipitate to serum I^{131} ratio and oxygen consumption. These factors acting together elevate blood pressure to a level near 180 mm. Hg. The mechanism by which this secondary elevation of blood pressure occurs must await further detailed study.

SUMMARY

The thyroid gland plays an important secondary role in the development of renal hypertension in the rat. Thyroid activity, as assessed by the ratio of thyroid weight to body weight, precipitate to serum I^{131} ratio and mean thyroid acinar cell height, increases sharply as systolic blood pressure level approaches 150 to 160 mm. Hg, i.e., the range of pressure usually considered to represent the high range of normotension and the low range of hypertension. The ratio of heart weight to body weight increases in a sigmoid-like fashion with increasing blood pressure and in an exponential fashion with increasing thyroid weight ratio. It is suggested that a mechanism(s) independent of thyroid gland activity increases blood pressure to levels of 150 to 160 mm. Hg. At this pressure level, thyroid gland activity increases and further elevates blood pressure to hypertensive levels.

ACKNOWLEDGMENT

It is a pleasure to acknowledge the guidance of Dr. Joseph Gennaro, Jr. of the Department of Anatomy in the handling and use of radioactive iodide. Mr. A. Kolwicz rendered valuable technical assistance.

REFERENCES

1. BRAUN-MENÉNDEZ E. Tiroides e hipertension nefrogena experimental. *Rev. Soc. argent. biol.*, 30: 138, 1954.
2. FREGLY, M. J. Effects of propylthiouracil on the development and maintenance of renal hypertension in rats. *Am. J. Physiol.*, 194: 149, 1958.
3. FREGLY, M. J. Prevention of salt hypertension by propylthiouracil treatment in rats. *Proc. Soc. Exper. Biol. & Med.*, 102: 299, 1959.
4. ABRAMS, M. and SOBIN, S. Latex rubber capsule for producing hypertension in rats by perinephritis. *Proc. Soc. Exper. Biol. & Med.*, 64: 412, 1947.
5. FREGLY, M. J. A simple and accurate feeding device for rats. *J. Appl. Physiol.*, 51: 539, 1960.
6. LAZAROW, A. Design and construction of metabolism cages. *Methods M. Res.*, 6: 215, 1954.
7. FRIEDMAN, M. and FREED, S. C. Microphonic manometer for indirect determination of systolic blood pressure in the rat. *Proc. Soc. Exper. Biol. & Med.*, 70: 670, 1949.
8. ADOLPH, E. F. Oxygen consumption of hypothermic rats and acclimatization to cold. *Am. J. Physiol.*, 161: 359, 1950.
9. VAN MIDDLESWORTH, L., NURNBERGER, C. E. and LIPSCOMB, A. Simplified sensitive test for thyroid function using protein-bound I^{131}. *J. Clin. Endocrinol.*, 14: 1056, 1954.
10. FREGLY, M. J., BAKER, M. I. and GENNARO, J. F., JR. Comparison of effects of thyroidectomy with propylthiouracil treatment on renal hypertension in rats. *Am. J. Physiol.*, 198: 4, 1960.
11. FREGLY, M. J. and COOK, K. M. Role of the thyroid gland in development and maintenance of renal hypertension in rats. *Acta Endocrinol.*, 34: 411, 1960.
12. BREWSTER, W. R., JR., ISAACS, J. P., OSGOOD, P. F. and KING, T. L. The hemodynamic and metabolic interrelationships in the activity of epinephrine, norepinephrine and the thyroid hormones. *Circulation*, 13: 1, 1956.
13. PAGE, I. H. and MCCUBBIN, J. W. Influence of thyroidal function on vascular reactivity in dogs. *Circulation*, 5: 390, 1952.
14. SMITH, D. Variations in vascular reactivity produced by season, cold stress and immaturity; role of thyroid and adrenal cortex. *Am. J. Physiol.*, 172: 118, 1953.

Plasma Corticosterone Levels and Salt Intake in Experimental Hypertension in the Rat*

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PRODUCTION OF experimental hypertension in the rat under conditions of increased adrenal cortical secretory activity in response to nonspecific stress generally has met with only limited success.[1–3] On the other hand, daily subcutaneous injections of 5 mg. of corticosterone to uninephrectomized female rats drinking a 1 per cent saline solution has induced severe and rapidly progressive hypertensive vascular disease.[4] One milligram daily of the steroid has failed to cause these changes.[4,5] In terms of the best estimate which can be made of the secretion of corticosterone under stress,[6,7] both doses of the steroid are large; indeed, the larger dose is equivalent to administering 3.5 gm. to a person weighing 70 kg. It seemed appropriate, therefore, to study the plasma corticosterone levels produced by the administration of sufficient amounts of this steroid to produce hypertensive disease and to compare these levels with those obtained in response to stress and ACTH. This became possible with the development of fluorometric methods by which small amounts of corticosterone could be rapidly and accurately determined.[8–10] This paper is a report of our preliminary observations in this area.

METHODS AND RESULTS

EXPERIMENTS 1 AND 2

Methods: In the *first* experiment, groups of twenty-four female rats of the Holtzman strain were submitted to stress by bilateral fracture of the tibia and fibula under ether anesthesia at four different times. Thirty, 60 and 120 minutes after stress, groups of eight rats were decapitated, blood was collected from the severed neck in heparinized beakers and plasma was obtained as rapidly as possible following centrifugation in the cold. For control purposes plasma was similarly obtained from 8 nonstressed rats after 12 hours isolation in a dark, quiet environment. The corticosterone levels in plasma were determined by a modification of the fluorometric procedure of Zenker and Bernstein.[9] The validity of this procedure for the measurement of corticosterone was tested by analyzing aliquots of plasma pools from stressed rats by both the fluorometric method and by isotopic dilution technics[11] using corticosterone-4-C.[14]‡ These studies showed that corticosterone accounted for 97 per cent of the values obtained by our modification of the Zenker and Bernstein fluorometric procedure when the nonspecific plasma fluorescence[10,12] was subtracted from the fluorometer readings.

The *second* experiment was performed to determine the levels of plasma corticosterone produced by ACTH stimulation of the adrenal cortex in hypophysectomized rats. Two groups of sixty rats, hypophysectomized 5 days previously, were injected subcutaneously with 1 I.U. and 8 I.U. of ACTH (Acthar® gel), respectively. At 0.5, 1, 3, 6, 12 and 24 hours after injection, ten rats from each group were killed by decapitation and plasma obtained as before. Plasma was obtained similarly from two groups of ten untreated hypophysectomized rats, one group of animals having been killed at the start of the experiment and the other group 24 hours later.

Results: The plasma corticosterone levels which occurred in response to stress (experiment 1) and to exogenous administration of ACTH (experiment 2) are depicted in Figures 1 and 2, respectively. The maximum levels resulting from this stress were far greater than those obtained with the dosages of ACTH employed. It is worthy of note that the difference in response to 1 I.U. and 8 I.U.

‡ Kindly supplied by The Steroid Allocation Committee of the Endocrinology Study Section, U. S. Public Health Service.

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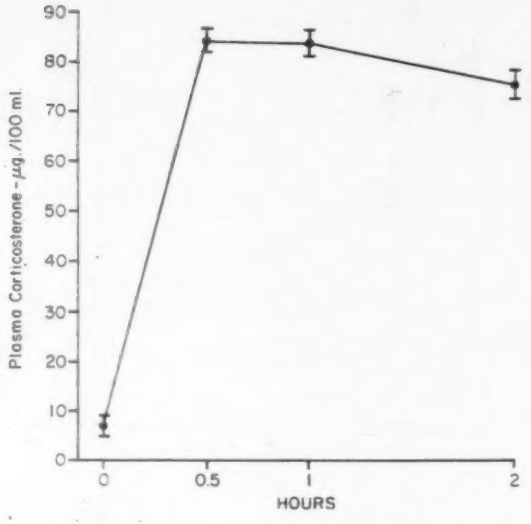

FIG. 1. Plasma levels of corticosterone following exposure of adult female rats to acute nonspecific stress (experiment 1). Each point is the mean of thirty-two values. The vertical bars represent two standard errors of the mean.

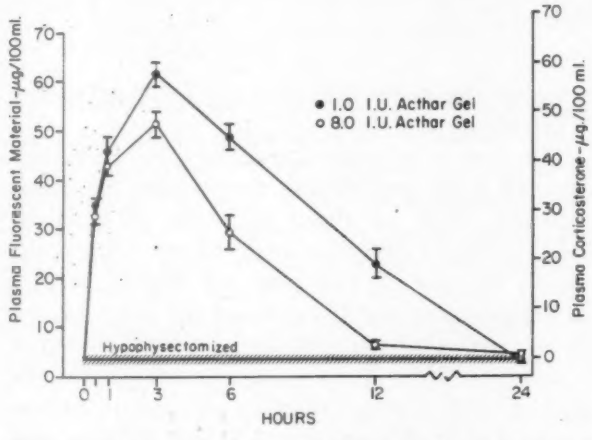

FIG. 2. Plasma levels of total fluorescent material and corticosterone in hypophysectomized adult female rats following subcutaneous injection of long-acting ACTH (experiment 2). The vertical bars represent two standard errors of the mean.

of ACTH is not so much in magnitude as in duration. Even with the higher dose, however, plasma corticosterone levels returned to zero within 24 hours.

EXPERIMENT 3

Methods: In order to determine the dosage of corticosterone and frequency of administration to be used in subsequent experiments, plasma levels were determined in three groups of adrenalectomized rats following single subcutaneous doses of 1, 2.5 and 5 mg. of corticosterone per 100 gm. body weight, administered as microcrystalline suspensions in distilled water. At intervals of 1, 3, 6, 12, 24 and 48

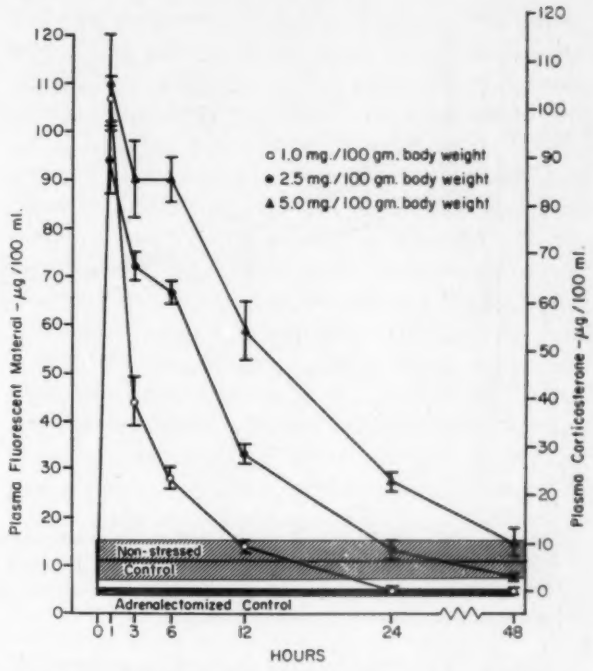
Plasma Fluorescent Material - µg./100 ml.
Plasma Corticosterone - µg./100 ml.
o 1.0 mg./100 gm. body weight
• 2.5 mg./100 gm. body weight
▲ 5.0 mg./100 gm. body weight
Non-stressed Control
Adrenalectomized Control
HOURS

FIG. 3. Plasma levels of total fluorescent material and corticosterone in adrenalectomized adult female rats following subcutaneous injection of various dosages of corticosterone as a microcrystalline suspension in water (experiment 3). The vertical bars represent two standard errors of the mean.

hours after injection, six rats from each group were decapitated and the plasma was collected as in experiment 1. Plasma was obtained similarly from six untreated, adrenalectomized rats and six nonstressed intact animals after 12 hours isolation in a dark, quiet environment.

Results: Plasma corticosterone levels produced by the single subcutaneous injection of these doses of steroid are shown in Figure 3. The difference in response to the three dose levels seems to be one of duration rather than height of initial elevation of corticosterone in the plasma. These results led us to choose 2.5 mg. and 1.25 mg. per 100 gm. of body weight as the dosages of corticosterone to be used in experiments 4 and 5.

EXPERIMENTS 4 AND 5

Methods: In the *fourth* experiment, fifty female rats weighing 80 to 100 gm. were bilaterally adrenalectomized and uninephrectomized, given Purina laboratory chow to eat and 1 per cent sodium chloride solution to drink *ad libitum*. Two days postoperatively approximately 0.8 ml. of blood was collected from the tail of ten rats and plasma obtained as before. The remaining forty rats received 2.5 mg. of corticosterone per 100 gm. body weight, and plasma from the tail was obtained in a similar fashion from

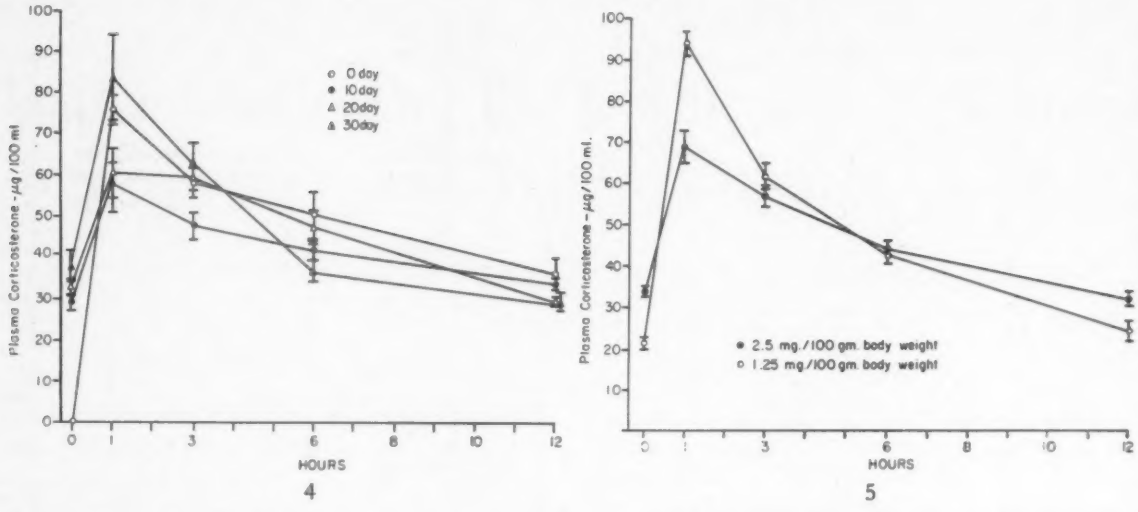

FIG. 4. Plasma levels of corticosterone in uninephrectomized, adrenalectomized female rats drinking 1 per cent sodium chloride solution *ad libitum* and injected with 2.5 mg. of corticosterone per 100 gm. body weight every 12 hours (experiment 4). Each point represents the average value for ten rats. The vertical bars represent two standard errors of the mean.

FIG. 5. The mean plasma corticosterone curves for experiments 4 and 5 show the fluctuations in plasma corticosterone for the 12 hour period following injection. Each point is the mean of thirty to forty values. The vertical bars represent two standard errors of the mean.

each of ten rats at intervals of 1, 3, 6 and 12 hours. Throughout the remainder of the experiment this dosage of corticosterone was injected subcutaneously into all fifty animals every 12 hours. At 10, 20 and 30 days blood from the tail was collected immediately before injection and at 1, 3, 6 and 12 hours after injection for determination of corticosterone content of plasma. Blood pressure was measured by the method of Friedman and Freed[13] with the rats under light ether anesthesia.

The *fifth* experiment was performed in the manner of experiment 4, except for the dosage of corticosterone which was reduced to 1.25 mg. per 100 gm. body weight every 12 hours.

Results: Contrary to expectations there was little or no cumulative effect of either dose of corticosterone on the plasma levels attained. This is shown in Figure 4, depicting plasma corticosterone concentrations as determined at the designated intervals during the 12 hour period after injection of 2.5 mg. of corticosterone per 100 gm. body weight at 0, 10, 20 and 30 days of the experiment. From these data from experiment 4 and similar results obtained in experiment 5, a mean response curve was determined for each dose of corticosterone (Fig. 5). These curves may be considered to represent the mean 12 hour fluctuations in plasma corticosterone which occurred throughout each experiment. Other than the first hour after injection there was no difference between the curves despite the different doses of steroid.

The mean plasma corticosterone level for each 12 hour period was determined from the response curve obtained at 0, 10, 20 and 30 days in both experiments. These values are shown in the upper part of Figure 6. A laboratory accident invalidated the data for the 10 day period of experiment 5; hence, no value is shown. From these data the over-all mean plasma corticosterone level was determined to be 46 ± 1.6 (S.E.) µg. per 100 ml. in the rats receiving 2.5 mg. of corticosterone per 100 gm. body weight, and 48.2 ± 2.9 (S.E.) µg. per 100 ml. in those injected with 1.25 mg. of corticosterone per 100 gm. body weight. The difference is not significant. Despite this fact, a slight but significant difference exists between the mean blood pressure levels of the rats in the two experiments, as shown in the lower part of Figure 6.

COMMENTS

In the induction of hypertensive vascular disease by adrenal steroids, administration has been either by subcutaneous implantation of pellets or by injection of a microcrystalline suspension. Almost uniformly a smaller amount of steroid has been required to produce hypertensive disease with the pellets than with the

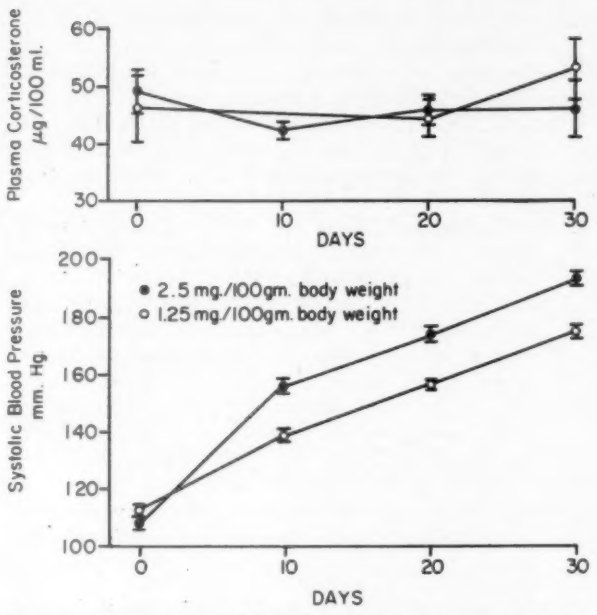

FIG. 6. Upper part of figure depicts the mean 12 hour plasma corticosterone levels as determined at intervals during each experiment. Lower part of figure shows the mean blood pressure levels of the rats throughout each experiment. The vertical bars represent two standard errors of the mean.

administration of a microcrystalline suspension, when all other experimental conditions were identical. Despite these extensive studies, data on the blood level of any of the corticoids used to produce hypertensive disease have not appeared. Two recent events combined to make possible the studies now reported in preliminary form. One was the development of a sensitive fluorometric procedure for the measurement of corticosterone[8,10] and the other was the report[4] that this steroid, the principal secretory product of the adrenal cortex of the rat, could induce hypertensive disease when given in sufficient quantity. The large amount of corticosterone seemingly required for the production of hypertension suggested that either very high blood levels were necessary or that much of the administered steroid remained unabsorbed. The observation that certain nonspecific stresses induced high plasma corticosterone levels while stress, generally, has been unsuccessful in causing equivalent hypertensive disease[3] seemed to favor the first possibility. On the other hand, the presence at necropsy of obviously unabsorbed corticosterone beneath the skin of hypertensive animals clearly favored the second possibility.

The foregoing findings reveal that the dosage of corticosterone employed in these experiments did not induce excessively high levels of the hormone in plasma. Indeed, the mean maximum postinjection level (92.6 ± 5.8 μg. per 100 ml. plasma) which occurred at 1 hour, was not significantly higher than that produced by a severe nonspecific stress (84.0 ± 2.3 μg. per 100 ml. plasma) and the calculated mean plasma level for all rats in both experiments was well below this. Thus, these observations have established that hypertensive disease can be induced by plasma levels of this naturally-occurring steroid which are well within the physiologic range. Also, they show that the injection of 8 I.U. of long acting ACTH produced over a 12 hour period a mean plasma corticosterone level of 39.8 ± 3.3 μg. per 100 ml., which is not far below the mean levels in the hypertensive animals of experiments 4 and 5. In contrast, the injection of 1 I.U. of ACTH gel produced a significantly lower ($p < 0.01$) mean plasma corticosterone level (25.8 ± 4 μg. per 100 ml.). Perhaps these findings account for the occurrence of moderately severe hypertensive disease following the daily administration of 10 I.U. of ACTH gel[14] and the failure of lower doses to induce such changes.[15] Quantitative measurement of plasma corticosterone levels during the development of ACTH-induced hypertensive disease forms a part of our studies in this area.

A reciprocal or complementary relationship between the regenerating adrenal cortex and sodium chloride intake in the genesis of hypertension has been shown by Oelsner and Skelton.[16] A similar relationship has been shown for desoxycorticosterone acetate[17] and adrenal cortical extract.[18,19] It had been hoped that the dosage differential in the present experiments might have shown a similar relationship between the actual plasma level of corticosterone and the intake of sodium chloride. However, despite the different doses of corticosterone in the last two experiments, the plasma levels of this steroid were identical. Hence, the difference in blood pressure observed in these experiments is probably due to differences in sodium chloride consumption since free access to saline drinking solution was allowed. Recent experiments support this assumption, for when mean plasma level of corticosterone is kept constant the blood pressure rise varies directly with the intake of sodium chloride.

SUMMARY

Plasma corticosterone levels were determined in uninephrectomized, adrenalectomized rats

during development of corticosterone-induced hypertensive vascular disease. The mean maximum plasma corticosterone concentration (92.6 μg. per 100 ml.) occurred 1 hour after subcutaneous injection of the steroid. This level was not significantly different from that observed (84 μg. per 100 ml.) in normal rats 1 hour after exposure to nonspecific stress. The mean plasma levels of corticosterone in hypertensive rats receiving 2.5 mg. and 1.25 mg. per 100 gm. body weight were 46 and 48.2 μg. per 100 ml., respectively. These values are well within the physiologic range attained during response to stress and only slightly higher than the mean 12 hour levels produced by 8 I.U. of long-acting ACTH. The significant difference observed between the blood pressures of animals receiving 2.5 mg. and 1.25 mg. of corticosterone twice daily is presumed to be due to difference in salt consumption.

References

1. Selye, H. On production of malignant hypertension by chronic exposure to various damaging agents. *Rev. canad. biol.* 2: 501, 1943.
2. Crane, W. A. J. and Ingle, D. J. Pathologic changes in sensitized rats exposed to stress. *Endocrinology*, 62: 474, 1958.
3. Hall, C. E. and Hall, O. Augmentation of hormone-induced hypertensive cardiovascular disease by simultaneous exposure to stress. *Acta endocrinol.*, 30: 557, 1959.
4. Skelton, F. R. Production and inhibition of hypertensive disease in the rat by corticosterone. *Endocrinology*, 62: 365, 1958.
5. Selye, H. and Heuser, G. Fourth Annual Report on Stress, p. 550. Montreal, 1954. Acta, Inc.
6. Singer, B. and Stack-Dunne, M. P. The secretion of aldosterone and corticosterone by the rat adrenal. *J. Endocrinol.*, 12: 130, 1955.
7. Chappel, C. I., Rona, G. and Browne, J. S. L. Possible role of increased sensitivity to adrenal steroids in adrenal-regeneration hypertension. *Canad. J. Biochem. & Physiol.*, 39: 453, 1961.
8. Silber, R. H., Busch, R. D. and Oslapas, R. Practical procedure for estimation of corticosterone or hydrocortisone. *Clin. Chem.* 4: 278, 1958.
9. Zenker, N. and Bernstein, D. E. The estimation of small amounts of corticosterone in rat plasma. *J. Biol. Chem.*, 231: 695, 1958.
10. Guillemin, R., Clayton, G. W., Smith, J. D. and Lipscomb, H. S. Measurement of free corticosteroids in rat plasma: physiological validation of a method. *Endocrinology*, 63: 349, 1958.
11. Hyde, P. M. and Skelton, F. R. Influence of stress on plasma and adrenal corticosterone levels in rats with intact and regenerating adrenals. *Endocrinology*, 69: 250, 1961.
12. Fortier, C. and DeGroot, J. Adrenohypophysial corticotrophin and plasma free corticosteroids during regeneration of the enucleated rat adrenal gland. *Am. J. Physiol.*, 196: 589, 1959.
13. Friedman, M. and Freed, S. C. Microphonic manometer for indirect determination of systolic blood pressure in the rat. *Proc. Soc. Exper. Biol. & Med.*, 70: 670, 1949.
14. Masson, G. M. C. and Corcoran, A. C. Hormonal influences on adrenal regeneration hypertension. *Arch. internat. pharmacodyn.*, 114: 322, 1958.
15. Skelton, F. R. Unpublished observations.
16. Oelsner, T. and Skelton, F. R. Complementary role of adrenal cortex on salt in adrenal-regeneration hypertension. *Am. J. Physiol.*, 200: 759, 1961.
17. Selye, H., Stone, H., Timiras, P. S. and Schaffenburg, C. Influence of sodium chloride upon the actions of desoxycorticosterone acetate. *Am. Heart J.*, 37: 1009, 1949.
18. Crane, W. A. J., Porter, R. E. and Ingle, D. J. Pathologic changes in adrenalectomized, sensitized rats treated with adrenal cortex extract. *Endocrinology*, 64: 215, 1959.
19. Crane, W. A. J. and Ingle, D. J. Pathogenic effects of salt loading in the presence and absence of the adrenal glands. *Endocrinology*, 65: 693, 1959.

Experimental Hypercholesterolemia from Chronic Excess Salt Feeding*

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THE PATHOGENESIS OF both hypertension and atherosclerosis remains unsettled; therefore, it is not surprising that the interrelationship of the two diseases is obscure. Most observers would probably agree that the diseases share no common etiology but that hypertension both hastens the onset of atherosclerosis and speeds its progress.[1]

My interest in salt intake in the etiology of human essential hypertension has been summarized in another paper in this seminar.[2] As part of the program to explore the relationship between dietary salt and hypertension, we have been studying the effects of chronic excess salt feeding in man and several species of animal for some years. Recent observations on rats and dogs indicate that such a feeding regimen is capable of elevating plasma lipids to a significant degree.[3] I am aware of no evidence which suggests that this mechanism is operative in man, or that it is involved in the pathogenesis of either human or experimental atherosclerosis. Nonetheless, in view of the widespread curiosity concerning factors which affect lipid metabolism in atherosclerosis, these observations may be of interest. Furthermore, if dietary salt is involved in the pathogenesis of hypertension[4–7] the present studies provide at least speculation on a basic link between hypertension and atherosclerosis.

EXPERIMENTAL PROCEDURE

Details are presented in the original paper on this subject.[3] Only a brief summary is included here, sufficient to clarify the general experimental procedure.

Animals and Diets: All of the rats were Sprague-Dawley females. They were started on the experimental regimen at an age of from 3 weeks to $2^1/_2$ months and subsequently continued without change for periods ranging from 2 to $15^1/_2$ months. Each experimental group had appropriate control animals, the basic diet of which consisted of Ralston Purina fox chow pellets without added sodium chloride; our analyses indicated that this food had 0.50 to 0.75 per cent sodium chloride. Test animals received the same chow to which one of two supplementary sodium-containing salts had been added by the manufacturer so that the final concentration calculated as sodium chloride approximated 8 per cent by weight. One of the salts was chemically pure sodium chloride, whereas the other was a mixture derived by evaporating sea water and hence called "sea salt" in this paper.† Our analyses indicated that the first of these salt-containing foods ("8 per cent NaCl food") contained an average of 8.1 per cent NaCl, whereas the other ("11.6 per cent sea salt food") contained about 7.3 per cent. The rationale of using sea salt to induce experimental hypertension is treated in another paper in this seminar.[8] All animals were housed in air-conditioned rooms, two to six animals per cage, with free access to drinking water and food. Weights and blood pressures were measured at approximately monthly intervals. Food consumption was checked over 4 day periods from time to time and, in association with parallel weight and growth curves, suggested similar amounts of food were being consumed by all groups.

The dog colony consisted of seventeen purebred beagles including sixteen females and one castrated male. Each animal was fed daily and consumed an average of 200 gm. of kibble, 100 gm. canned horse meat and 1 teaspoonful of a low sodium mineral-vitamin supplement. The five *control* animals received this diet plus tap water *ad libitum*. The four "1 per cent NaCl-H_2O" animals ate the same diet but drank 1 per cent saline *ad libitum* in place of tap water. The four "2 per cent NaCl food" animals and the four "6 per cent NaCl food" animals were fed kibble to which NaCl had been added in amounts calculated to be 2 and 6 per cent, respectively.

† I am indebted to the Trace Elements Corporation, Houston, for a supply of Admiral brand trace element sea salt sufficient to initiate these experiments.

* From The Medical Research Center, Brookhaven National Laboratory, Upton, New York. Supported by the United States Atomic Energy Commission.

TABLE I

Group 1. Female Rats, Eighteen Months of Age at Sacrifice

Rat No.	Food	Months on Diet	Body Weight (gm.)	Systolic Blood Pressure (mm. Hg)	Blood Urea Nitrogen (mg. per cent)	Total Cholesterol (mg. per cent)
1	Control	17½	306	123	...	95
2	Control	17½	302	109	9.1	95
3	Control	17½	342	125	10.2	75
4	Control	17½	270	96	...	92
5	Control	17½	312	109	19.4	106
Average (and S.D.)			*306.4 (±25.7)*	*112.4 (±11.9)*	*12.9*	*92.6 (±11.2)*
6	11.6 per cent sea salt	15½	268	160 (3)*	11.1	121 (2)
7	11.6 per cent sea salt	15½	326	177 (3)	...	193 (3)
8	11.6 per cent sea salt	15½	235 (2)	157 (3)	12.7	400 (3)
9	11.6 per cent sea salt	15½	252 (2)	125	...	115 (3)
10	11.6 per cent sea salt	15½	314	159 (3)	10.3	160 (3)
11	11.6 per cent sea salt	15½	272	130	...	198 (3)
12	11.6 per cent sea salt	15½	236 (3)	166 (3)	10.8	100
13	11.6 per cent sea salt	15½	267	144 (2)	10.3	210 (3)
14	11.6 per cent sea salt	15½	332	133	...	125 (2)
15	11.6 per cent sea salt	15½	223 (3)	162 (3)	8.6	441 (3)
16	11.6 per cent sea salt	15½	243 (2)	151 (3)	17.2	380 (3)
Average (and S.D.)			*269.8 (±38.2)*	*151.3 (±16.4)*	*11.6 (±2.8)*	*222.1 (±74.8)*

Systolic blood pressures are the average of last three values, obtained at monthly intervals.

* Differs from mean value in control groups by 2 or 3 S.D., respectively. Salt-fed group had significantly ($p < 0.01$) higher mean systolic blood pressure and plasma cholesterol than control group.

FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

Analyses of these foods in our laboratory gave the following sodium concentrations, calculated as NaCl: unmodified kibble, 1 per cent; 2 per cent NaCl kibble, 2.5 per cent; 6 per cent kibble, 6 per cent; horse meat, 0.5 per cent. The animals receiving added sodium chloride began eating it at 2½ to 4½ months of age and at the time of the blood lipid and blood pressure measurements upon which this report is based, they had completed from 45 to 48 months on this regimen. The four animals in the 6 per cent NaCl food group received 2 per cent NaCl food during the first 7½ months of the experiment after which they received the 6 per cent food.

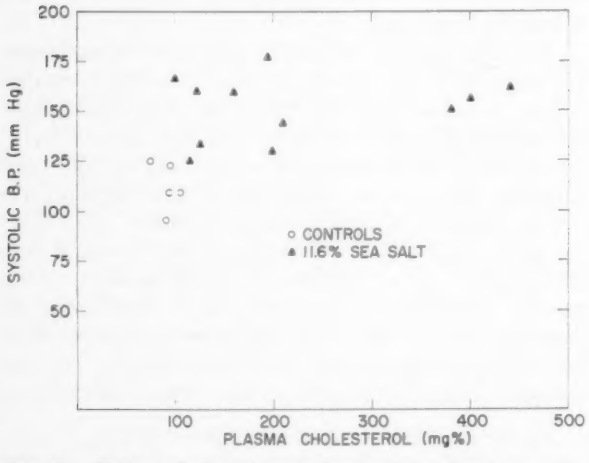

FIG. 1. Effect of chronic salt feeding on blood pressure and plasma cholesterol levels in female rats. Results after 15½ months. From: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

Blood Pressure Measurements: For both rats and dogs, the microphonic method of Friedman and Freed[9] was used with the modifications as described.[3]

Miscellaneous Methods: Blood was obtained from rats by nicking the tail, from dogs by venepuncture, and in both instances was put directly into heparinized tubes which were immediately centrifuged and the plasma removed. Cholesterol was measured by the technic of Abell et al.[10] and blood urea nitrogen by Conway's microdiffusion technic.[11] Statistical significance of the difference between means of groups was calculated by Student's test using the modern tables of Fisher and Yates.[12]

RESULTS

RATS

Group 1 (Table I, Fig. 1): The salt-fed animals had received extra salt for about 15½ months when the final measurements shown in Table

TABLE II

Group 2. Female Rats, Seven and One-Half Months of Age at Time of Bleeding for Plasma Cholesterol

Rat	Food	Months on Diet	Body Weight (gm.)	Systolic Blood Pressure (mm. Hg)	Total Cholesterol (mg. per cent)
16	Control	7	297	114	113
17	Control	7	297	124	63
18	Control	7	232	124	81
19	Control	7	268	126	81
20	Control	7	242	120	99
21	Control	7	269	126	125
22	Control	7	255	123	113
23	Control	7	292	132	90
24	Control	7	263	124	89
25	Control	7	260	137	63
26	Control	7	285	138	94
Average (and S.D.)			*269.1 (±21.8)*	*126.2 (±7.1)*	*91.9 (±19.9)*
27	11.6 per cent sea salt	6½	262	154 (3)*	125
28	11.6 per cent sea salt	6½	249	122	138 (2)
29	11.6 per cent sea salt	6½	263	180 (3)	125
30	11.6 per cent sea salt	6½	239	120	119
31	11.6 per cent sea salt	6½	283	166 (3)	113
32	11.6 per cent sea salt	6½	249	172 (3)	71
33	11.6 per cent sea salt	6½	281	162 (3)	123
34	11.6 per cent sea salt	6½	245	182 (3)	132 (2)
35	11.6 per cent sea salt	6½	263	136	106
36	11.6 per cent sea salt	6½	275	162 (3)	123
37	11.6 per cent sea salt	6½	265	170 (3)	113
38	11.6 per cent sea salt	6½	239	135	85
39	11.6 per cent sea salt	6½	271	194 (3)	143 (2)
40	11.6 per cent sea salt	6½	264	120	96
41	11.6 per cent sea salt	6½	256	130	125
Average (and S.D.)			*260.3 (±14.0)*	*153.7 (±24.6)*	*115.8 (±19.5)*
42	8 per cent NaCl	6½	277	140 (2)	109
43	8 per cent NaCl	6½	270	190 (3)	155 (3)
44	8 per cent NaCl	6½	254	145 (2)	90
45	8 per cent NaCl	6½	270	148 (3)	106
46	8 per cent NaCl	6½	258	138	113
47	8 per cent NaCl	6½	263	142 (2)	90
48	8 per cent NaCl	6½	253	150 (3)	104
49	8 per cent NaCl	6½	271	138	113
50	8 per cent NaCl	6½	247	124	99
51	8 per cent NaCl	6½	268	116	73
52	8 per cent NaCl	6½	268	134	106
53	8 per cent NaCl	6½	222 (2)	126	90
54	8 per cent NaCl	6½	245	126	99
55	8 per cent NaCl	6½	267	132	91
56	8 per cent NaCl	6½	225 (2)	153 (3)	99
Average (and S.D.)			*257.2 (±16.5)*	*140.1 (±17.3)*	*101.8 (±18.6)*

Systolic blood pressures are those for the last month of the experiment.

* Differs from mean value in control group by 2 or 3 S.D., respectively. Both salt fed groups had higher mean blood pressure (sea salt < 0.01, NaCl $< 0.05 > 0.01$) than control group. Sea salt group only had higher ($p < 0.01$) mean plasma cholesterol than control group.

FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

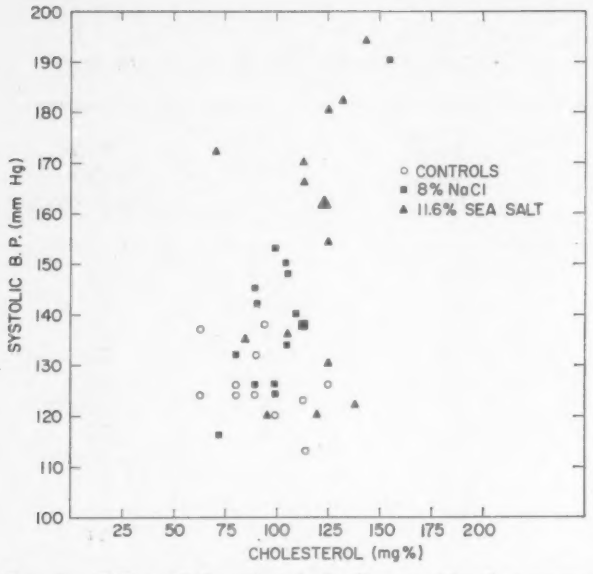

FIG. 2. Effect of chronic salt feeding on blood pressure and plasma cholesterol levels in female rats. Results after $6^1/_2$ months. FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

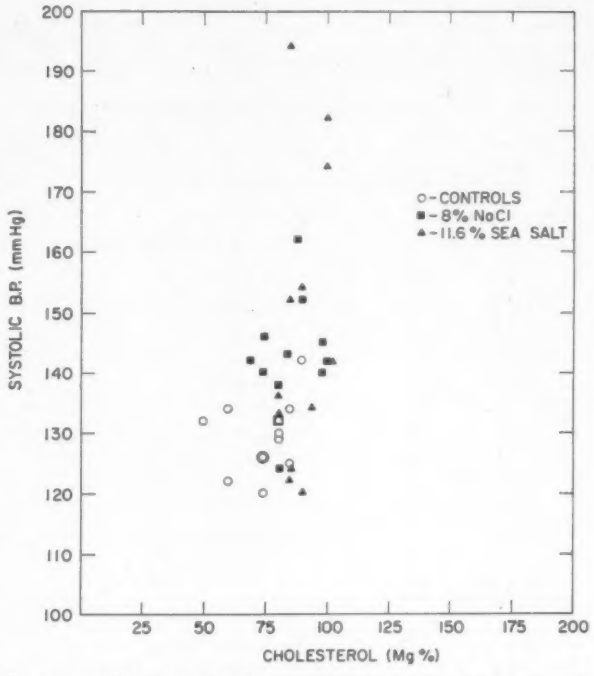

FIG. 3. Effect of chronic salt feeding on blood pressure and plasma cholesterol levels in female rats. Results after 2 months. FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

I were obtained. The average blood pressure and systolic pressure were higher in the salt-fed group (p less than 0.01) than in the control group. However, in individual animals there did not appear to be a direct correlation between increase in pressure and increase in plasma cholesterol, as exemplified by rats 11 and 14 which had nearly identical blood pressures but rat 14 had more than four times the plasma cholesterol concentration of 11. Inspection of the graph (Fig. 1) shows similar if lesser disparities. Neither blood pressure nor cholesterol concentration was correlated with weight or blood urea nitrogen.

Group 2 (Table II, Fig. 2): The two test groups had been fed extra salt for about $6^1/_2$ months at the time of the determination of blood pressure and plasma cholesterol concentration shown in Table II. Among individual salt-fed animals, elevations in systolic pressure were common whereas elevations in plasma cholesterol were not. Among the sixteen rats with significantly elevated blood pressures only three also had increased plasma cholesterol; a single animal (No. 28) had normal pressure but a slightly increased plasma cholesterol (p less than 0.05). These data suggested that if salt-feeding were to result frequently in hypercholesterolemia, a period longer than 6 months was commonly required. No correlations with weight were evident.

Group 3 (Table III, Fig. 3); The test animals in this group had received extra salt for only 2 months and, in support of this deduction relative to length of time required to elevate plasma cholesterol concentration, individual significant elevations were present in only four animals, all of which were included among the thirteen salt-fed animals with elevated systolic pressures. Again, no correlations could be established with weight or blood urea nitrogen.

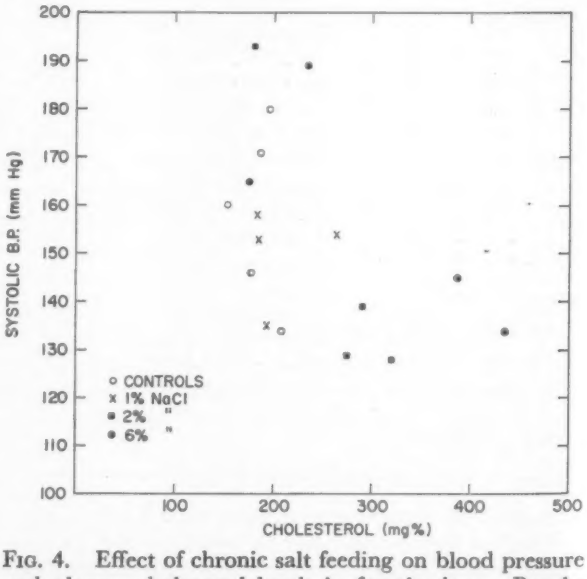

FIG. 4. Effect of chronic salt feeding on blood pressure and plasma cholesterol levels in female dogs. Results after 4 years. FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

TABLE III

Group 3. Female Rats, Eleven Weeks of Age When Blood for Plasma Cholesterol Obtained and Systolic Blood Pressures Measured

Rat	Food	Body Weight (gm.)	Systolic Blood Pressure (mm. Hg)	Blood Urea Nitrogen (mg. per cent)	Total Cholesterol (mg. per cent)
57	Control	191	122	18.7	60
58	Control	225	126	17.4	74
59	Control	204	125	29.7	85
60	Control	210	126	20.9	74
61	Control	200	130	19.6	81
62	Control	215	142 (2)*	18.6	90
63	Control	209	129	...	81
64	Control	222	132	...	50
65	Control	223	120	...	74
66	Control	225	134	...	85
67	Control	235	132	...	81
68	Control	240	134	...	60
Average (and S.D.)		*216.6 (±14.4)*	*129.3 (±6.0)*	*20.8 (±4.5)*	*74.6 (±.121)*
69	11.6 per cent sea salt	210	194 (3)	13.0	85
70	11.6 per cent sea salt	181 (2)	133	21.6	81
71	11.6 per cent sea salt	218	134	18.4	94
72	11.6 per cent sea salt	201	152 (3)	20.9	85
73	11.6 per cent sea salt	214	182 (3)	23.4	100 (2)
74	11.6 per cent sea salt	215	154 (3)	17.8	90
75	11.6 per cent sea salt	189	122	...	85
76	11.6 per cent sea salt	211	174 (3)	...	100 (2)
77	11.6 per cent sea salt	205	136	...	81
78	11.6 per cent sea salt	175 (2)	120	...	90
79	11.6 per cent sea salt	201	124	...	81
80	11.6 per cent sea salt	197	142 (2)	...	101 (2)
Average (and S.D.)		*201.4 (±13.8)*	*147.3 (±24.6)*	*19.2 (±3.7)*	*89.4 (±7.7)*
81	8 per cent NaCl	190	124	19.3	81
82	8 per cent NaCl	203	152 (3)	26.8	90
83	8 per cent NaCl	233	138	19.5	81
84	8 per cent NaCl	208	143 (2)	40.4	84
85	8 per cent NaCl	204	146 (2)	41.6	74
86	8 per cent NaCl	241	132	31.0	81
87	8 per cent NaCl	220	140	...	98
88	8 per cent NaCl	213	142 (2)	...	100 (2)
89	8 per cent NaCl	212	142 (2)	...	69
90	8 per cent NaCl	179 (2)	162 (3)	...	88
91	8 per cent NaCl	225	145 (2)	...	98
92	8 per cent NaCl	215	140	...	74
Average (and S.D.)		*211.9 (±17.2)*	*142.2 (±9.4)*	*29.8 (±9.8)*	*84.8 (±10.2)*

All rats were on the diets for 2 months.

* Differs from control mean value by 2 or 3 S.D. respectively. Both salt-fed groups had higher mean blood pressures and plasma cholesterol concentrations compared with the control group: *blood pressure*, sea salt, $p < 0.05 > 0.01$; NaCl, $p < 0.01$; *cholesterol*, sea salt, $p < 0.01$; NaCl, $p < 0.05 > 0.01$. The mean *weight* of the group fed sea salt was significantly less than the control group: $p < 0.05 > 0.01$.

FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[3]

DOGS

The control and salt-fed groups did not differ significantly in mean systolic blood pressures; furthermore, among individual members with elevated pressure, no correlation with plasma cholesterol concentration was apparent (Table IV, Fig. 4). Among the twelve animals which were fed extra salt seven had an increase in cholesterol of which all but one exceeded three standard deviations of the

TABLE IV
Seventeen Beagles Fed Diets Containing Different Amounts of NaCl for Four Years

Dog	Food	Age (mo.)	Mo. on Diet	Body Weight (kg.)	Systolic Blood Pressure (mm. Hg)	Blood Urea Nitrogen (mg. per cent)	Total Cholesterol (mg. per cent)	Phospholipids (mg. per cent)	Total Cholesterol/ Phospholipid	Triglycerides (mg. per cent)
1	Control	52	50	8.5	160	17.5	153	...	...	...
2	Control	52	50	10.6	134	10.3	208	...	...	...
3*	Control	52	50	10.2	180	12.1	195	440.0	0.45	18.1
4	Control	52	50	13.9	146	9.4	177	358.0	0.49	20.4
5†	Control	41	40	9.6	171	11.6	186	...	...	...
Average (and S.D.)				*10.6 (±2.0)*	*158 (±19)*	*12.2 (±3.2)*	*184 (±21)*	...	...	...
6	6 per cent NaCl	49	45‡	7.5	165	9.3	175	...	...	...
7	6 per cent NaCl	49	45	11.8	145	12.7	386 (3)§	618.0	0.63	18.7
8	6 per cent NaCl	49	45	11.0	134	30.4	435 (3)	687.8	0.63	29.3
9	6 per cent NaCl	49	45	16.8	189	11.5	233 (2)	...	...	...
Average (and S.D.)				*11.8 (±3.8)*	*157 (±24)*	*16.0 (±8.7)*	*307 (±123)*	...	...	...
10	2 per cent NaCl	50	45	13.4	193	10.8	180	...	...	...
11	2 per cent NaCl	49	45	11.4	129	12.3	275 (3)	...	...	...
12	2 per cent NaCl	49	45	13.1	128	10.3	320 (3)	602.5	0.51	70.4
13	2 per cent NaCl	49	45	9.3	139	11.5	290 (3)	476.0	0.61	19.9
Average (and S.D.)				*11.8 (±1.9)*	*147 (±30)*	*11.2 (±0.9)*	*266 (±61)*	...	...	...
14	1 per cent NaCl	52	48	8.4	135	12.7	193	...	...	...
15	1 per cent NaCl	52	48	9.1	153	11.2	185	...	...	...
16	1 per cent NaCl	52	48	14.2	154	12.3	264 (3)	479.0	0.55	17.3
17‖	1 per cent NaCl	52	48	13.6	158	9.1	183	385.2	0.48	11.6
Average (and S.D.)				*11.3 (±3.0)*	*150 (±10)*	*11.3 (±1.6)*	*208 (±39)*	...	...	...

All dogs females except 17 (1 per cent NaCl).
* Dog 3 impregnated by No. 17 and delivered two pups at age 11 months.
† Offspring of No. 3.
‡ First $7^1/_2$ months, all 6 per cent NaCl dogs received 2 per cent NaCl food, so time on 6 per cent NaCl food was $37^1/_2$ months.
‖ Male, castrated at age of 9 months.
§ Differs from mean control value by 2 or 3 S.D., respectively. Blood pressures not significantly different among groups. Mean cholesterol of 2 per cent NaCl group significantly higher ($p < 0.05 > 0.01$) than control group. The large coefficient of variation (40 per cent) in 6 per cent NaCl group probably contributes to the mean cholesterol level not being significantly greater than that of control group.
FROM: DAHL, L. K. *J. Exper. Med.*, 112: 635, 1960.[8]

mean value in the control animals. In two animals from each group, plasma phospholipids and triglycerides were measured in addition to cholesterol.* These data as well as the calculated total cholesterol/phospholipid (TC/PL) ratios are shown in the last three columns of Table IV. By the same method for analysis of phospholipids, normal dogs were observed to have serum concentrations of 362 mg. per cent[13] and a TC/PL ratio of 0.41. In that study, total cholesterol was analyzed by a method[14] which yields slightly lower values than that used in our study so that it would be

* For these determinations, I am greatly indebted to Drs. Howard A. Eder and Lewis Gidez of the Department of Medicine, Albert Einstein College of Medicine.

expected, as found, that the normal TC/PL ratio derived from the present technics would be somewhat higher than 0.41. One dog (No. 12, 2 per cent NaCl) was found to have a markedly elevated triglyceride value of 70.4 mg. per cent. Although this is a limited sample, there is suggestive evidence that other plasma lipids may increase in response to the same stimulus that resulted in hypercholesterolemia.

Comments

The present observations indicate that experimentally produced chronic excess salt feeding may result in hypercholesterolemia; there is suggestive evidence that other plasma lipids may share in this response. Chronicity of feeding is clearly important: rats which had eaten extra salt for periods up to 6 months had relatively infrequent and only modest elevations, whereas rats and dogs fed added salt for more than 1 and 4 years, respectively, frequently had marked elevations in plasma cholesterol. Further confirmation has been observed in studies now being prepared for publication. In one such study, by making consecutive measurements on the same animals over a period of about 1 year it was found that after 9 or 10 months of salt feeding, 40 per cent of the members of a large colony of rats had plasma cholesterol values ranging from 150 to 516 mg. per cent.

It is of some interest that plasma lipids were not increased equally among members of two of the groups of dogs which were ingesting roughly equivalent amounts of salt, as 1 per cent NaCl drinking solution for one group and, in the other, as 6 per cent NaCl food. Animals which obtained their salt primarily as 1 per cent saline solution seemed to have less significant elevations than those which consumed it in their food. The latter animals drank about 50 per cent more water than did those drinking 1 per cent saline but whether this difference is important cannot be said at present.

The role of hypertension *per se* in the elevation of plasma lipids observed in some of these animals is not entirely clear. In the rats, separation of elevated pressure from elevated lipids is made particularly difficult because of the frequency with which salt feeding is associated with some degree of hypertension. In our experience, about four rats in five will have hypertension of mild to severe degree when they are chronically on one of the salt regimens used by us. Therefore in such a group the probability of any single animal with hypercholesterolemia also having hypertension would be high. In this case, although a high correlation would exist it would not necessarily indicate a causal relationship between the two observed phenomena; it is also possible that both were the result of a common stimulus (excess salt consumption) in which case the elevated pressure would not be the *cause* of the elevated lipids.

Fortunately, some clarification of this problem is provided by observations on the dogs. In our animals, salt-feeding did not appear to induce hypertension, presumably because of the profound capacity of dogs to excrete oral salt loads quickly.[15] Among the seven dogs with significantly elevated plasma cholesterol concentrations, only one was definitely hypertensive (No. 9, 6 per cent NaCl group) and a second was borderline (No. 16, 1 per cent NaCl group): these two animals had the lowest cholesterol levels among the seven with elevations.

Whether hypertension can be a primary cause of elevated serum lipids is not clear from a recent extensive review of the literature.[16] On the whole, it is fair to say that most of the available experimental data suggest that hypertension *per se*, probably will not *cause* an elevation in plasma lipids,[17–20] although some of the data are equivocal. Thus, Lewis, Green and Page [21] found that changes did not develop in dogs with neurogenic hypertension, whereas comparable animals with nephrogenic hypertension had elevated serum lipoproteins; the latter elevations were interpreted to be related to the kidney damage associated with the renal hypertension rather than the hypertension itself. Katz and Stamler[22] induced hypertension in cockerels by substituting 0.9 per cent saline for drinking water or by feeding up to 8 per cent NaCl in the food; they observed neither hypercholesterolemia nor enhanced atherosclerosis in the animals receiving extra salt. Meneely and his associates[23,24] observed elevated serum cholesterol levels in the rats chronically fed excess salt, but concluded that the correlation was more striking with blood pressure than with salt consumption.

Deming et al.[25] studied the effect of experimental hypertension on induced atherosclerosis in the rat. Among animals on an atherogenic regimen, there was a positive correlation between increase in blood pressure and increase

in serum cholesterol concentration. However, in evaluating the effect of salt, they found that it was "not possible to conclude from these results that salt alone has no effect on cholesterol concentration . . ." (Experiment 3). Donomae et al.[26] induced atherosclerosis in rabbits by feeding lanolin which in six instances was supplemented with added NaCl. Among these six animals were those with the highest concentration of serum cholesterol in the series of fifty-two rabbits.

At the present time no explanation is at hand for the mechanism by which hypercholesterolemia is induced with chronic salt-feeding. The possible role of the kidney is suggested by the nephrotic syndrome in man; furthermore, Meneely found that some of his salt-fed rats had a clear-cut nephrotic-like syndrome.[23,24] However, this was not observed in any of the animals in this series although we have seen it occasionally in others. Furthermore, as judged by the blood urea nitrogen concentration in our animals, significant kidney disease was not present. At the present time an extensive histologic and histochemical review of tissues from these and other rats on the same regimen is being made. Preliminary observation suggests no clear-cut correlation between pathologic changes and hypercholesterolemia, although final judgment must await conclusion of the study. In any event, the kidney cannot be ruled out at the present time.

In the absence of facts to the contrary, it is permissible to speculate on possible mechanisms. It should be clearly stated in advance that our own prejudices are against rather than for kidney damage being the cause of the hyperlipemia here. Variation in exogenous supplies of cholesterol probably need not be seriously considered since the only known variable was the added salt and this did not affect food consumption significantly. It is more intriguing to me, at least, to account for these lipid changes on the basis of enhanced intestinal absorption, increased synthesis or decreased degradation, or possibly some combination of these. In line with such an interpretation, the instillation of water or salt solution into the gastrointestinal tract is used by lymph physiologists to enhance intestinal lymphatic flow.[27,28] Theoretically it is possible that increased lymphatic flow could result in an increase in effective absorption from the gut as well as an increased hepatic lymph flow, possibly with an attending increase in synthesis of cholesterol.

From these studies it cannot be concluded, or even inferred, that chronic excess salt consumption is involved in the pathogenesis of atherosclerosis either in experimental animals or in man. In fact, in the experimental studies mentioned,[22,25,26] the authors specifically stated that there was no increase in the atherosclerosis as a result of salt-feeding. Nonetheless, since chronic excess salt consumption is capable of elevating plasma lipids, it could conceivably affect the atherosclerotic process as well. It is rather unlikely that salt consumption could play a primary role in atherosclerosis, but it might play an accessory role in an organism on an atherogenic regimen such as that of the inhabitants of most western societies. It is important to remember that slight abnormalities operating over decades can result in significant disease. Such a potential may exist here.

Summary and Conclusions

Female rats and dogs which had consumed excess salt for periods of about 1 and 4 years, respectively, frequently had increases in plasma cholesterol concentration, sometimes quite marked.

Chronicity of feeding appeared to be critical for development of the hypercholesterolemia since rats on the same regimen for only 2 or 6 months had less frequent and less marked elevations.

The evidence at hand suggests that the lipid changes were not related primarily to increased blood pressure, kidney disease, differences in food consumption or in body weight.

There is no indication that excess salt consumption is related to atherogenesis although a factor capable of elevating plasma lipids conceivably could affect the atherosclerotic process.

References

1. Katz, L. N. and Stamler, J. Experimental Atherosclerosis, p. 59. Springfield, Ill. 1953. Charles C Thomas.
2. Dahl L. K. The possible role of chronic excess salt consumption in the pathogenesis of essential hypertension. *Am. J. Cardiol.*, 8: 571, 1961.
3. Dahl, L. K. Effects of chronic excess salt feeding. Elevation of plasma cholesterol in rats and dogs. *J. Exper. Med.*, 112: 635, 1960.
4. Dahl, L. K. and Love, R. A. Evidence for relationship between sodium (chloride) intake and human essential hypertension. *Arch. Int. Med.*, 94: 525, 1954.
5. Dahl, L. K. and Love, R. A. Etiological role of sodium chloride intake in essential hypertension in humans. *J.A.M.A.*, 164: 397, 1957.
6. Dahl, L. K. Salt intake, adrenocortical function

and hypertension. *Nature, London*, 181: 989, 1958.

7. Dahl, L. K. Salt intake and salt need. *New England J. Med.*, 258: 1152, 1205, 1958.
8. Dahl, L. K. and Heine, M. The enhanced hypertensogenic effect of sea salt over sodium chloride. *Am. J. Cardiol.*, 8: 726, 1961.
9. Friedman, M. and Freed, S. C. Microphonic manometer for the indirect determination of systolic blood pressure in the rat. *Proc. Soc. Exper. Biol. & Med*, 70: 670, 1949.
10. Abell, L. L., Levy, B. B., Brodie, B. B. and Kendall, F. E. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J. Biol. Chem.*, 195: 357, 1952.
11. Conway, E. J. Microdiffusion Analysis and Volumetric Error, ed. 3 (revised), pp. 152–164. London, 1950. Crosby Lockwood and Son, Ltd.
12. Fisher, R. A. and Yates, F. Statistical Tables, ed. 3, p. 1. New York, 1948. Hafner Publishing Co., Inc.
13. Havel, H. J., Eder, H. A. and Bragdon, J. H. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. *J. Clin. Invest.*, 34: 1345, 1955.
14. Sperry, W. M. and Webb, M. A revision of the Schoenheimer-Sperry method for cholesterol determination. *J. Biol. Chem.*, 187: 97, 1950.
15. Ladd, M. and Raisz, L. G. Response of the normal dog to dietary sodium chloride. *Am. J. Physiol.*, 159: 149, 1949.
16. Waris, E. Studies on serum lipids and lipoproteins in hypertension. *Acta med. Scandinav., suppl.* 337, 161: 79, 1958.
17. Page, I. H. The relationship of the extrinsic renal nerves to the origin of experimental hypertension. *Am. J. Physiol.*, 112: 166, 1935.
18. Dill, L. V. and Isenhour, C. E. Occurrence of atheroma in the aorta in rabbits with renal hypertension. *Arch. Path.*, 33: 655, 1942.
19. Rodbard, S. and Freed, S. C. The effect of desoxycorticosterone acetate on the blood pressure of the dog. *Endocrinology*, 30: 365, 1942.
20. Wilens, S. L. The effect of postural hypertension on the development of atheromatosis in rabbits fed cholesterol. *Am. J. Path.*, 19: 293, 1943.
21. Lewis, L. A., Green, A. A. and Page, I. H. Ultracentrifuge lipoprotein pattern of serum of normal, hypertensive and hypothyroid animals. *Am. J. Physiol.*, 171: 391, 1952.
22. Stamler, J. and Katz, L. N. The effect of "salt" hypertension on atherosclerosis in chicks fed mash without a cholesterol supplement. *Circulation*, 3: 859, 1951.
23. Meneely, G. R., Tucker, R. G., Darby, W. J. and Auerbach, S. Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and of a syndrome of edema and renal failure. *J. Exper. Med.*, 98: 71, 1953.
24. Meneely, G. R. and Ball, C. O. T. Experimental epidemiology of chronic sodium chloride toxicity and the protective effect of potassium chloride. *Am. J. Med.*, 25: 713, 1958.
25. Deming, Q. B., Mosbach, E. H., Bevans, M., Daly, M. M., Abell, L. L., Martin, E., Brum, L. M., Halpern, E. and Kaplan, R. Blood pressure, cholesterol content of serum and tissues, and atherogenesis in the rat. *J. Exper. Med.*, 107: 581, 1958.
26. Donomae, I., Matsumoto, Y., Kokubu, T. and Koide, R. Production of coronary heart disease in the rabbit by lanolin feeding. *Circulation Res.*, 5: 645, 1957.
27. Watkins, A. L. and Fulton, M. N. The effect of fluids given intraperitoneally, intravenously and by mouth on the volume of thoracic duct lymph in dogs. *Am. J. Physiol.*, 122: 281, 1938.
28. Simmonds, W. J. The effect of fluid, electrolyte and food intake on thoracic duct lymph flow in unanesthetized rats. *Australian J. Exper. Biol. Med. Sc.*, 32: 295 1954.

Panel Discussion

Chairman: Dr. James Conway

DISCUSSION OF PAPERS BY TOBIAN; ISLER; FREGLY AND GONZALEZ; SKELTON; AND DAHL

FLOYD SKELTON: Dr. Tobian, how long a time elasped between removal, perfusion and measurement of the juxtaglomerular cell index in your experiments? What was the time relationship between measurement of the juxtaglomerular cell index in the perfused kidney and the control kidney? If there was a significant lapse of time between fixation of the kidneys, could it be that the fall in juxtaglomerular cell index of the perfused kidneys is due simply to the fact that it is an *in vitro* organ and may not be considered entirely physiologic any longer? The stainability of the granules might be influenced by these factors instead of, or as well as, by perfusion pressure. I wonder, too, whether the perfusion was performed with extremely low pressures to see if hypergranularity resulted? If the kidney were truly alive, one might expect to find such hypergranularity in response to low pressure perfusion.

LOUIS TOBIAN: One kidney was taken out as a control sample and the other kidney was transferred without a period of ischemia to a little box and then perfused for 3 hours with blood from a donor rat. Thus, it was getting blood which had been passing through a liver and a real lung, and so on. The low pressure perfusions were carried out for the same length of time as the high pressure perfusion. The low pressures were not more than 10 mm. Hg or so less than the mean pressure of a normal rat. If rough handling were a factor one would have expected the same loss of stainability in both the perfusions at normal and at high pressures. The ones which were perfused at 85 mm. Hg had no reduction in the number of granules; whereas the ones perfused at 180 did. I do not think that loss of stainability is the probable explanation for this difference. It could be that the perfusion at the higher pressure damaged the granules in a way that the perfusion at normal pressure did not; we have no real evidence for this. Remember, the kidneys in both types of perfusion were isolated for about the same length of time.

FLOYD SKELTON: Did you keep the first kidney in a chamber under relatively normal perfusion pressure and then take it out?

LOUIS TOBIAN: Yes.

FLOYD SKELTON: How about low pressure perfusion? Have you ever noted hypergranularity?

LOUIS TOBIAN: No. We have not tried that, although it is an interesting idea.

SYDNEY FRIEDMAN (Vancouver, Canada): Dr. Tobian's work on the juxtaglomerular apparatus represents some soul-satisfying pieces of investigaton, but I want to take issue with the part about volume receptors and stretch receptors. In strictly physical terms, when I think of a volume receptor, it is impossible to conceive of one without moving parts which will clearly measure the volume of the whole system without transducing it to some other variable such as pressure. When physiologists talk about a volume receptor, they mean something which measures the volume of the whole system without transducing it into a pressure change. If your definition is less rigid and you transduce (i.e., convert energy from one state to another) volume change to pressure change in the system, you would measure the volume of the system only if you could be absolutely certain that the particular location of the pressure receptor makes it reflect changes in the system as a whole. When physiologists talk of a stretch receptor or a pressure receptor, they mean precisely that. This is not the same as a volume receptor. I find a volume receptor a rather inconceivable entity. I rather agree with Dr. Burton on that particular point. If, on the other hand, one measures a change experimentally and finds that a certain physiologic variable seems to reflect a change in volume, then this only indicates a correlation with the change in volume. In other words, it is not the volume change itself that is being measured. Now, when Dr. Tobian speaks of a stretch receptor or pressure receptor in the glomerular arterioles, I think this is absolutely valid, but to change that over to a volume receptor would be for him to take on his shoulders all of the problems which attach to volume receptors.

My second point is totally distinct from the first, so I would like to bring this to Dr. Tobian's attention and ask for his comments. His experiments are distinct from those of Pitcock and Hartroft (*Am. J. Path.*, 34: 863, 1958), although parallel indeed, but he arrives at the conclusion that the basic change is a pressure one and that their responses to sodium manipulation can be understood in terms of pressure and volume. The Hartrofts take the opposite view; that is, the sodium change is primary and pressure changes is to be understood in terms of sodium distribution. I think both may in fact be interlocked since stretch itself is known to change membrane permeability. In fact, stretch can be used as an experimental tool for this. Would Dr. Tobian comment on the difference in emphasis of his view with that of the Hartrofts?

DAVID GORDON (Miami, Florida): I agree entirely with Dr. Friedman on the point of semantics about volume receptors and that it ought to be called the stretch receptor. But if it is a stretch-pressure-receptor, then it brings up the question as to how it responds to changes in salt intake. I can follow the argument about the effect of putting a clip on the renal artery and reducing pressure; therefore, stretch-receptor must shrink down or vice versa, but if it is not a volume receptor I do not understand how it responds to salt.

LOUIS TOBIAN: When I talk about a volume receptor, I am really referring to a stretch receptor that appreciates changes in volume. Under certain circumstances a stretch receptor can, indeed, change its degree of stretch in relation to a change in volume, but in other circumstances this would not necessarily be so. Whenever I said "volume receptor," I actually meant "stretch receptor." On the other hand, I do not see why *under certain circumstances* a stretch receptor cannot register volume. You can look at it the other way around; that is, in the sense of negative stretch or "unstretch." If I break your suspenders, they will change their stretch but in a negative direction.

GEORGE MENEELY (Nashville, Tennessee): That's like explaining obesity as the absence of negative calories!

LOUIS TOBIAN: I suppose I could use the word "distend" or "undistend," but if you take a distended rubber band and move the ends in relation to each other, you are changing the degree of stretch.

HOWARD SWANN (Galveston, Texas): An equivalent situation is a low pressure in the carotid sinus. This causes a lessening of the volleys of impulses in the sinus nerve, but even so, the lessening of impulses is a very powerful stimulus to the medullary vasomotor centers.

SYDNEY FRIEDMAN: Burton has put that fairly clearly. He points out that the tension operates both on the intraluminal pressure as well as the extraluminal pressure and it is really the net difference between the two which correlates with the tension of the wall. If you lower extraluminal pressure, you will increase the stretch of the wall, and if you increase that pressure, the wall tension will decrease.

LOUIS TOBIAN: You mentioned stretch versus sodium. I haven't talked with Mrs. Hartroft recently so I do not know her present position. There is an article in which she studied human subjects, and put great stress on the sodium concentration in the plasma (*Am. J. Path.*, 34: 863, 1958). We all agree on the facts; it is just how to interpret them. The nub of this disagreement would be brought out most clearly by a low salt diet. Both of us agree that salt increases the granulation; Hartroft would say that it did it somehow by changing the serum sodium concentration, and I would say that it did it by some other means. I cannot enthusiastically accept the change in sodium concentration as the major stimulus because when I put rats on a low salt diet, I am always amazed that their serum sodium concentration does not change. In these experiments the granulation goes up, but the extracellular sodium concentration may not change at all. It may change 1 mEq. per L, but the change is very, very tiny. Utilizing the perfusion set-up and knowing that I could drop the granulation in a couple of hours with high pressure perfusion, I perfused at normal pressure with blood containing about 190 mEq. of sodium and there was no degranulation. If the granular cells were really impressed with a high sodium concentration, this would give them a chance to show it, and they didn't show it. This is why I would tend to accept a stimulus that did not involve concentraton but rather some other parameter such as changes in volume which alter the stretch of the juxtaglomerular cells.

SIDNEY CASSIN (Gainesville, Florida): Dr. Tobian, would you comment on the effect of the pituitary and especially ACTH on juxtaglomerular granulation? In recent literature it is reported that ACTH increases granulation of the juxtaglomerular cells.

LOUIS TOBIAN: I am aware of this work. I personally can only report on three rats. I gave them a large dose of ACTH and their granules didn't change. Moreover, Hartroft tried a low salt diet in hypophysectomized rats and noted that they had a typical hypergranulation response in the absence of any ability to change their pituitary secretions. These experiences argue against an all-important role for ACTH. However, it may have some sort of minor role.

FLOYD SKELTON: I want to interject a reference on this subject by Marks et al. (*Proc. Soc. Exper. Biol. & Med.*, 105: 593, 1960). It looks quite interesting to me although it certainly differs from the opinions of others.

JAMES CONWAY (Ann Arbor, Michigan): I wonder whether Dr. Tobian has tried to differentiate between pulse pressure and mean pressure in his perfusion experiments?

LOUIS TOBIAN: It was mentioned that stretch may change membrane permeability. That is certainly a good possibility. We did not analyze pulse pressure versus mean pressure. We were just doing an initial experiment to see if anything at all would happen and never got beyond that stage.

Dr. Gordon, you ask how salt can affect a stretch receptor? If you eat more salt, this causes you to retain more water and swells your blood volume. Murphy (*J. Clin. Invest.*, 29: 912, 1950) has measured blood volumes of people who have different levels of salt intake and says that the blood volumes are different. The big question concerns the manner in which this extra blood volume is distributed. First, we must admit we do not know. Let us assume that it is distributed generally. We will assume that vascular volume increased by ten per cent and that every vascular element shared in the increase. We

will include the afferent arteriole in the list of vascular elements. The afferent arteriole would have to accommodate a 10 per cent increase in volume, and just as a balloon, it would be stretched. Since the juxtaglomerular cells are in the walls of the afferent arteriole, they too would be a little stretched. I admit that I do not know how this extra blood volume is accommodated. You might counter that it is all in the veins, and I could not say you are wrong.

DAVID BOHR (Ann Arbor, Michigan): I hate to see you abandon the volume receptor. I think it is a valuable concept to picture the sensing of a change in volume. Changes in both volume and pressure could be sensed by the same type of stretch receptor. The volume receptor is merely a pressure receptor that happens to be in the distensible tube. If on the other hand this same sensing device happens to be in a poorly distensible tube, it becomes a pressure receptor. I think the dual terminology must be retained not only because one is influenced primarily by changes in volume while the other is influenced by pressure, but also because the effect of the former is to correct the volume change while the latter acts to correct the pressure change.

LOUIS TOBIAN: I think you can say it is a stretch receptor that can measure volume under certain circumstances. How do you like that?

DAVID BOHR: I think that one measures pressure and the other volume and their action is to correct the specific change that they sense.

DAVID GORDON: It would act a lot better if it were sitting on a vein.

GEORGE MENEELY: In the last analysis a volume receptor of any kind can only measure volume locally. It has got to be a stretch receptor. It is impossible that anything should sense the entire volume at any one site.

EDWARD P. RADFORD, JR. (Boston, Massachusetts): Does Dr. Tobian think there is a neural element in stimulation of the juxtaglomerular apparatus in response to pressure?

LOUIS TOBIAN: The juxtaglomerular complex is very rich in nerves. I do not know where the nerves fit into the whole picture. The cells appear to be secretory in type and are so richly intertwined with nerve elements that one wonders whether nervous influence might not really be important on the afferent side.

EDWARD P. RADFORD, JR.: This provides a way to bring neuroeffector agents into the picture, for example, the catecholamines.

HOWARD SWANN (Galveston, Texas): I would like to ask Dr. Tobian about how he applies his theory to glomerulonephritis. This disease usually puts a block in the renal vascular system downstream from the juxtaglomerular apparatus. This would result in a rise in pressure next to the juxtaglomerular apparatus which should cause, if his theory is correct, low blood pressure and not high blood pressure.

LOUIS TOBIAN: Dr. Swann, I cannot get around what you have mentioned. I am not sure glomerulonephritis works in just the same way.

JOHN WELLER (Ann Arbor, Michigan): If you have hypervolemia and acute glomerulonephritis I think it might well work the same way.

LOUIS TOBIAN: I do not understand how glomerulonephritis produces hypertension because it is not as pure a situation as is the experimental situation. If it affects the glomerulus only, then I would have a hard time fitting that into the juxtaglomerular theory.

JAMES CONWAY: I think it is a vascular disease generally and not a glomerular disease.

MELVIN FREGLY: Dr. Tobian, I wonder whether it is necessary to postulate any connection between renin release and aldosterone secretion in the etiology of hypertension. We have been able to produce hypertension consistently in the absence of the adrenal gland both with renal encapsulation and with salt loading (*Am. J. Physiol.*, 191: 542, 1957; *Endocrinology*, 66: 240, 1960). In addition to these are the studies Wilgram presented in this seminar (*Am. J. Cardiol.*, 8: 582, 1961).

LOUIS TOBIAN: When I talked about renin, I was talking only about one limited aspect, about one of the effects this might have on sodium excretion. Over and above that is its effect on high blood pressure, and this is a different consideration entirely.

ARTHUR CORCORAN (Cleveland, Ohio): I was interested that Dr. Tobian brought up renin and/or angiotensin stimulating the adrenal to secrete aldosterone or its equivalent. Do you visualize that as a direct stimulation? A good many years ago Masson and Deane gave renin and angiotensin to rats and found some hypertrophy of the zona glomerulosa. At that time we tried to explain it as a response to the saluretic effect of angiotensin and renin, which is demonstrable in rats (*Internat. Cardiol. Congress*, Paris, 1950). Now it seems it might even be a central effect of angiotensin; we did not work it out fully and I don't know that it has been worked out.

LOUIS TOBIAN: Drs. Corcoran, Masson and Deane were actually the first to bring out the principle that renin would stimulate the zona glomerulosa of an adrenal (*J. Clin. Endocrinol.*, 11: 193, 1951). This work has been relatively ignored until the last year or so. Hartroft has confirmed it. She admiñistered kidney extract and got a widening of the zona glomerulosa. More recent papers have dealt with the giving of renal extracts and angiotensin and noting that the aldosterone in the renal venous blood increases acutely. I am not certain whether this is a direct effect or not. This is a very new subject.

ARTHUR CORCORAN: It would seem that it might be indirect because of the central effect of angiotensin.

LOUIS TOBIAN: That may be. Investigators know that if they give renal extracts or angiotensin they get a rise in renal venous aldosterone output. At present that is where the subject rests.

DAVID GORDON: In connection with the paper of

Drs. Fregly and Gonzalez, I found interesting the transition point of 160 mm. Hg after which they began to find a larger thyroid gland. I have some evidence which also suggests that this is a transition pressure in my renal-hypertensive rats. If I have moderately renal hypertensive rats, the kidney with the clip on it has a normal or greater than normal size, but if I manage to get a higher pressure, the kidney begins to shrink. The point is that at about a pressure of 160 mm. Hg I suspect that renin is involved and is released. My question is, could the effect on the thyroid be some effect of renin rather than of blood pressure?

MELVIN FREGLY: Since angiotensin is a polypeptide (a decapeptide, which is converted into the active octapeptide), we wondered whether or not it might have a thyroid stimulating hormone-like activity and we are now in the process of testing that, but I can only speculate as yet. TSH is probably also a polypeptide so that the possibility exists that at the time the kidney may be producing a larger amount of renin and angiotensin these may be the substances stimulating the thyroid gland.

FLOYD SKELTON: I would like to comment on Dr. Isler's paper. New Orleans is not considered ordinarily to be a goiterous area. There is a lot of iodine in the food people eat. There is also a high content of sodium. A 2-year study one of the histologists has been making on adenomatous thyroids shows that in the autopsy population of the charity hospitals there is very high incidence of adenomatous nodular goiters. This is contrary to what he and most others would have expected. Would Dr. Isler like to comment on this?

ARTHUR CORCORAN: On Dr. Isler's paper, the renal reabsorption of iodide and thiocyanate tend to be diminished. If one diminishes the reabsorption of chloride by giving large doses of chloride, one can diminish thiocyanate reabsorption. I wonder if he isn't getting an ion entrainment by impairing reabsorption of iodide by the saluresis.

ARTHUR GROLLMAN (Dallas, Texas): Regarding the study on the thyroid, it seems to me one would anticipate that salt would not only affect the kidney and give animals hypertension but might also act on other organs just as violently as on the kidney. If one would study pancreatic function carefully under heavy salt loading, one might also show the effect of this extra stress, since each cell wherever it is in the body must extrude this ion from its interior.

Another point in connection with Dr. Isler's work: iodine is a halide, and we know that as far as the thyroid is concerned, big enough doses of bromide will act somewhat like iodide. As far as I know no one has studied the excretion of iodide to any extent, but we should expect the same relationship because these are all halides, thus accounting for the excess elimination of iodide. The effect of vasopressin on the collecting tubules is directed primarily against water, but this change in water permeability might also affect the permeability or the extrusion rate of iodide as well as chloride and might have some relationship to these very interesting results on the thyroid.

HENRI ISLER: The high incidence of thyroid adenomas in the New Orleans area is probably not due to the high sodium content of the drinking water. We have produced thyroid nodules in the rat by feeding them a low iodine diet (*J. Nat. Cancer Inst.*, 21: 1066, 1958; 23: 675, 1959). The diet we used contained 1 per cent sodium chloride. If we added iodine to the same diet sufficient to raise the iodine intake to an adequate level, very few nodules were observed, although the diet still contained 1 per cent sodium chloride. Nodule formation is linked with goiter. Therefore, sodium chloride may be expected to enhance nodule formation only when it enhances goiter production, that is, under conditions of low or critical iodine intake, but not when the iodine intake is high. The effect of salt fits into the frame of the etiology of iodine deficiency goiter. This etiology is sufficient to explain the only goitrous condition of the rat: parenchymatous or simple goiter. However, the situation is more complex in man as other types of goiter can be recognized for which the causes are poorly known. There is evidence that factors other than iodine deficiency may be important in the etiology of human goiter. Thus, Clements and Wishart (*Metabolism*, 5: 623, 1956) have shown that milk of cows fed on certain plants may contain goitrogens, which are probably responsible for endemic goiter observed in certain areas of Australia (e.g., in Tasmania).

High incidence of nodules has been reported in serially cut, clinically normal thyroid glands by Mortensen et al. (*J. Clin. Endocrinol Metab.*, 15: 1270, 1955). Thyroid nodules seem to be much more frequent than it was thought a few years ago. Tracing of the factors responsible for these nodules is a complex enterprise since the nodules found at death may have been formed at any time during life, and may have persisted after the conditions which induced their formation were reversed. Indeed, in rats we found that nodules formed under conditions of iodine deficiency persisted when this condition was reversed by iodine supplementation (*J. Nat. Cancer Inst.*, 23: 675, 1959).

Regarding the intrarenal mechanism by which sodium chloride induces heavy urinary losses of iodine, I think that impaired reabsorption by excess chloride may account for *some of our results*, but not for others, such as the effect of sodium bicarbonate and of vasopressin. The reabsorptive mechanism may be the one primarily involved, but clear-cut evidence is lacking.

FLOYD SKELTON: As for Dr. Dahl's paper, I wonder if the effect of sodium on the thyroid gland should not be considered also? Could it reduce thyroid uptake of iodine by increasing iodide excretion in the urine of the animals? Perhaps there is some degree of thyroid insufficiency. Could the hypercholesterolemia have been on this basis?

ARTHUR GROLLMAN: This comment is in reference

to the difficulty in rendering the dog hypertensive by feeding salt. Dr. Meneely showed some time ago that the amount of potassium in the diet certainly has great importance. I wondered if measurements were made of the potassium contents of the diets. Rat diets are lower in potassium than the dog diets since dogs usually get meat to eat. Is it possible that the high potassium intake of the dog protects it from becoming hypertensive? It is hard to see why the dog should be immune to this process. I believe we can accept potassium depletion as being equivalent to feeding high sodium. We have made dogs hypertensive by depleting puppies of potassium, which suggests that by giving enough sodium we should be able to make them hypertensive. An experiment that might be worthwhile would be to dialyze the food given the dog to get rid of the potassium and the sodium, then add sodium to the food and see if this will produce hypertension.

As regards the relationship between hypertension and atherosclerosis, there is a vicious cycle in the human, which is of significance clinically. If a patient has atherosclerosis which in turn affects the kidney with nephrosclerosis involving the smaller vessels of the kidney, we have the equivalent of the Goldblatt kidney and we should expect to get hypertension. If, on the other hand, we look upon hypertension as a vascular disease, we can understand why the hypertensive subject should be more prone to atherosclerosis. In actual practice what one sees in a patient who has had hypertension for a long time and lives long enough is that the patient has both atherosclerosis and hypertension. There are two processes in a vicious cycle and both are usually present in the same patient. In the lower animals which are less prone to atherosclerosis you have a purer form of hypertension and less atherosclerosis; but in the human being you tend toward a combination.

ARTHUR CORCORAN: Regarding Floyd Skelton's demonstration of less hypertension in the corticosteroid rats given 2.5 per cent salt, do you get *no* hypertension in the rats on very little salt diet? If you remember, Gaunt claimed that in corticosteroid hypertension there was not only a wide variation from rat to rat but also it was independent of salt intake within most ranges or within ranges that he studied. Masson also observed this. He could make rats hypertensive by giving them corticosteroids without large salt intakes. Do you find this?

In some patients with severe hypertension and atherosclerosis, lipoproteins and cholesterols decrease if the patient's blood pressure is decreased. It doesn't matter how you decrease the blood pressure; whether it is done with one drug or the other, anything that decreases the blood pressure tends to drop the cholesterol and beta-lipoprotein level in the hypertensive patient (*Ann. N. Y. Acad. Sc.*, 64: 620, 1956). Is this a simple matter of diminishing plasma filtration through arterioles? Diminishing the blood pressure does not usually lessen the renal lesions they already have and may only prevent the progress rather than remit their critical disease. The association is with severe hypertension clinically. It has been taken up by Deming and others; our observations and Schroeder's with angiotensin were taken up by Ciba, but actually we found other agents equally as effective as Apresoline.®

JAMES CONWAY: It has become fairly apparent that salt is a nephrotoxic agent in the manner in which it is being used; therefore, I think it important that the elevation in lipids be shown to be the results of proteinuria or a specific effect of the salt. Have you any data on plasma protein levels? If the elevation of phospholipids or cholesterol is the result of the nephrotic syndrome this would occur only after a depression of serum protein.

LEWIS DAHL: To Dr. Skelton's question relative to hypothyroidism: Until this morning I had been interpreting salt-feeding to the contrary. There are some very interesting data in the Japanese literature relative to the effect of salt feeding not producing hypothyroidism but hyperthyroidism or at least increasing the metabolic rate. Originally I became interested in the Japanese while reading, in a monograph on perspiration, that some northern Manchurians ate in excess of 40 gm. of salt a day during the winter, which is most of the year, in the belief that it kept them warm (KUNO, Y., Human Perspiration, p. 268. Springfield, Ill., 1956, Charles C Thomas). Ogata et al. (*Japanese J. Physiol.*, 2: 303, 1952) observed that the daily ingestion of up to 50 to 60 gm. of sodium chloride significantly increased the basal metabolic rate of young Japanese men; Maeda (*Bull. Res. Inst. Diath. Med.*, Kumamoto Univ. 8: 4, 1958) explored these findings using in vitro technics and observed that salt feeding enhanced the QO_2 of liver and muscle slices from rats and rabbits.

Relative to Dr. Grollman's question as to whether the dogs could be ingesting higher potassium than the rats and thereby getting more protection. I suppose this is possible but dietary analysis indicates that both rat and dog diets contain approximately the same per cent potassium.

To Dr. Corcoran: I think the question relative to hypertension primarily elevating plasma lipids is not really settled. I am sure you are aware of the massive review of the world literature that Waris did a few years ago (*Acta med. Scandinav., Suppl.* 337, 161: 79, 1958), from which it was concluded that the problem was unsettled. My own personal evidence is derived from the Japanese we studied in Hiroshima several years ago, some of whom had high blood pressures with no elevation in plasma lipids.

To Dr. Conway: We have not measured plasma proteins in our animals. We have not had the nephrotic syndrome. Histologically we do not seem to see any difference between the animals with elevation in cholesterol and those without. Nonetheless, I do think it is fair to say that we cannot rule out some much more subtle factor in the kidney.

Some Observations on the Role of Added Supplements of Sodium and Lithium in the Pathophysiology of Corticoid and Metacorticoid Hypertension in the Rat*

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SINCE THE discovery that certain adrenal corticoids are capable of causing hypertension which, together with the associated vascular aberrations, is aggravated by increasing sodium intake,[1–4] much interest has centered upon the role of this cation in various forms of clinical and experimental hypertensive disease. This was given further impetus by the findings of Sapirstein,[5] Meneely,[6] Koletsky,[7] and others, that sodium chloride alone, if chronically consumed in sufficient quantity, caused hypertensive cardiovascular disease.

The type and distribution of vascular lesions caused in the rat by sodium excess cannot be distinguished from those produced more rapidly by simultaneous treatment with sodium surfeit and desoxycorticosterone acetate (DCA). On the other hand, the complete elimination of sodium from the diet protects the rat from the cardiovascular effects of steroid overdosage.[8]

These data, collectively, indicate that sodium, or some aspect of its metabolism, may be the protagonist in the genesis of these experimental forms of hypertensive cardiovascular disease, a conclusion supported by the findings that DCA hypertension is minimized or prevented by agents which facilitate renal excretion of sodium or retard its absorption in the gut.

Lithium chloride was considered useful in the treatment of hypertensive patients on a low sodium diet until its toxic effects became apparent. Fregly[9] has shown that adrenalectomized rats demonstrate no appetite for lithium chloride (LiCl), and that the electrolyte fails to protect against adrenal insufficiency. However, Duliere[10] demonstrated that LiCl could be substituted for NaCl in frog heart perfusion media. Radomsky et al.[11] noted that the simultaneous administration of DCA failed to influence the serum electrolyte profile, serum lithium levels or lithium toxicity in dogs fed LiCl. Thus, although Li can replace Na in some biologic processes it cannot in others. Because of the close chemical relationship between the cations, it seemed of value to ascertain what effect the substitution of LiCl for NaCl would have on the course of DCA overdosage in the uninephrectomized rat.

The third experiment herein reported deals with another aspect. Recently we have reported that it is possible to produce hypertensive cardiovascular disease in hypophysectomized rats by DCA and NaCl.[12] It was of interest to determine whether this condition was dependent upon continued administration of steroid and salt, or whether a true "self-sustained" or metacorticoid hypertension could be developed and sustained in the absence of added dietary sodium.

MATERIALS AND METHODS

In the first experiment forty-two female Holtzman rats weighing 90 to 110 gm. were uninephrectomized and divided into four groups. Group 1, containing eleven animals, received a solution of LiCl to drink and 1 mg. per day of a microcrystalline DCA suspension subcutaneously; group 2, ten animals, received LiCl solution only; group 3, eleven animals, received NaCl drinking fluid and 1 mg. per day of

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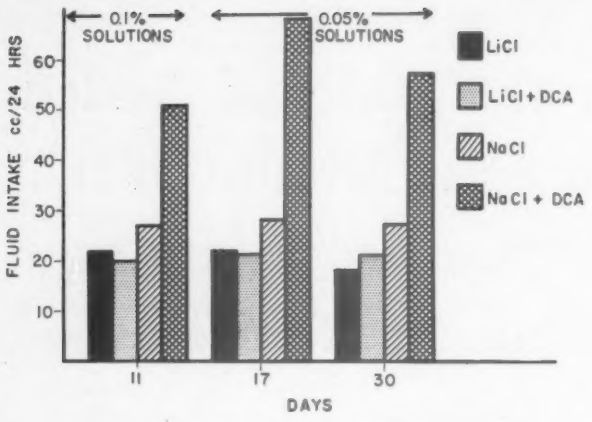

FIG. 1. Group average daily fluid consumption of DCA-treated and untreated rats consuming LiCl or NaCl solutions. This figure is reproduced by permission of the editor of *Laboratory Investigation*.

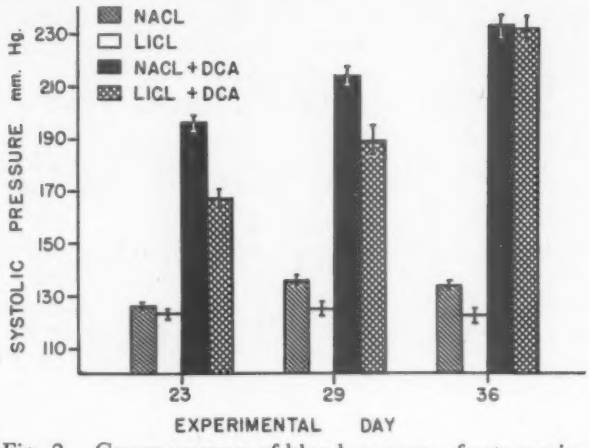

FIG. 2. Group average of blood pressure of rats receiving NaCl and LiCl with and without concurrent administration of DCA.

DCA; and group 4, ten animals, received only the NaCl solution.

The solutions were given *ad libitum*. The initial concentration of each solution was 0.85 per cent of the salt, but the rats drank almost none of the LiCl solution and lost weight. Hence, the concentration of both electrolyte solutions was progressively decreased until, by the fifteenth day, they were reduced to 0.05 per cent; at which level normal growth of those drinking LiCl was resumed. Purina laboratory chow was fed *ad libitum*. Body weight was taken weekly and 24 hour fluid intake measured periodically. Blood pressure of unanesthetized animals was measured by tail plethysmography or by a microphonic method; pressures exceeding 150 mm. Hg systolic were interpreted as reflecting hypertension. The experiment was terminated on the thirty-ninth day and various tissues were removed for weight and histologic examination.

The second experiment used slightly smaller female rats (80 to 90 gm). These were uninephrectomized and divided into four groups. Group 1 contained nine animals, each of which received 1 mg. per day DCA and 0.05 per cent LiCl solution *ad libitum;* group 2 contained nine animals on the same steroid dosage, but given distilled water to drink. The amount ingested was restricted to that which animals of group 1 voluntarily consumed. Group 3, eight animals, received the same steroid treatment and distilled water *ad libitum*, group 4, six animals, received only distilled water *ad libitum*. Purina laboratory chow was freely available at all times. Blood pressure and body weight were periodically measured as previously indicated and the experiment was terminated on the twenty-eighth day. Organs and tissues were taken for weight and histologic examination. In both experiments vascular lesions were arbitrarily graded on a 0 to 3 scale and the severity was recorded as the aggregate figure expressed as a percentage of the possible maximum.

RESULTS

EXPERIMENT 1

In the first experiment, animals receiving LiCl each consumed 15 to 35 cc. per day of the solution. Rats given DCA consumed no more than untreated rats, and neither group increased intake as the experiment progressed. Intake of NaCl solution in untreated rats was also relatively stable during the experiment, but at a slightly higher level of 20 to 50 cc. per rat per day. Steroid treatment increased intake to between 30 to 140 cc. per rat per day, the low figure representing early consumption and the large, the greater intake later in the experiment. Fluid intake is given in Figure 1.

Blood Pressure: All animals treated with DCA became hypertensive and to about the same degree, regardless of whether LiCl or NaCl was being consumed. Animals on LiCl alone had slightly lower pressures than those on NaCl alone (Fig. 2). Growth appeared to be somewhat retarded by LiCl, particularly when DCA was also given.

There was a greater mortality among DCA-treated rats receiving NaCl than among those receiving LiCl. Five of the eleven animals on NaCl died during the course of the experiment, whereas only one of eleven on LiCl succumbed.

Organ Weights: The adrenal weight of animals treated with DCA and NaCl was less than that of NaCl-treated control rats. No such difference was evident when glands from LiCl and LiCl plus DCA animals were compared. In contrast to rats receiving DCA plus NaCl, LiCl alone caused no adrenal hypertrophy; animals treated with it did not exhibit adrenal atrophy when DCA was superimposed.

TABLE I

Effect of Drinking LiCl and NaCl Solutions with and without Simultaneous Desoxycorticosterone (DCA) Administration in the Rat

Data	Group and Treatment			
	1 (LiCl + DCA)	2 (LiCl)	3 (NaCl + DCA)	4 (NaCl)
No. rats				
Initial	11	10	11	10
Final	10	9	6	10
Body weight (gm.)				
Initial	99 ± 2*	103 ± 2	99 ± 1	102 ± 2
Final	174 ± 7	194 ± 4	202 ± 3	211 ± 4
Organ weight (mg./ 100 gm. body weight)				
Adrenal	39.6 ± 2.3	38.2 ± 0.8	32.9 ± 1.9	38.5 ± 1.4
Thymus	244 ± 14	225 ± 9	182 ± 11	195 ± 10
Heart	465 ± 15	326 ± 5	461 ± 10	308 ± 5
Kidney	1226 ± 32	883 ± 28	1176 ± 41	907 ± 39
Vascular lesions				
Heart				
% Incidence	100	0	83	0
% Severity	57	0	39	0
Kidney				
% Incidence	100	0	100	0
% Severity	80	0	66	0
Panarteritis†				
% Incidence	70	0	33	0
% Severity	40	0	17	0

* Weights given with standard error of the mean.
† Pancreatic and mesenteric.

The hearts and kidneys were both enlarged in DCA-treated hypertensive rats, and to the same degree in those receiving LiCl as in those which had received the NaCl solution.

There was no clear-cut effect of any form of treatment on the weight of the thymus.

Vascular Lesions: The hearts, kidneys and sections from the pancreatic and mesenteric vascular beds were examined microscopically. Nephrosclerosis was slightly more severe in DCA-treated animals receiving LiCl than in those receiving NaCl, with about the same percentage incidence. The same was true of cardiac myocarditis and/or vascular necrosis. Both incidence and severity of periarteritis were greater in hypertensive animals which had received LiCl than in those treated with NaCl (Table I).

EXPERIMENT 2

In the second experiment, response to LiCl and DCA was somewhat different. The animals were slightly smaller than in the first experiment and it was evident that four animals grew well, whereas five others did not. The former became hypertensive and the latter

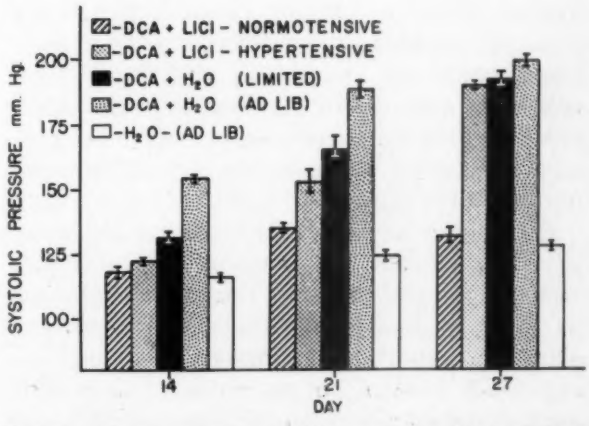

FIG. 3. Group average systolic pressure of rats treated with DCA and either LiCl solution, limited water intake or unlimited water intake, and of untreated control rats.

TABLE II

Effect of DCA on Body and Organ Weight, Blood Pressure and Vascular Pathology of Rats Drinking LiCl or Distilled Water

Data	Treatment				
	Desoxycorticosterone				Control
	LiCl		Water		Water (ad libitum)
	Ad libitum		Limited	Ad libitum	
No. rats					
Normotensive	...	5	0	0	6
Hypertensive	4	...	9	8	0
Body weight (gm.)					
Initial	86 ± 1*	85 ± 1	86 ± 1	85 ± 1	85 ± 1
Final	162 ± 5	103 ± 5	179 ± 3	196 ± 4	194 ± 6
Organ weight (mg./100 gm. body weight)					
Adrenals	36.9 ± 1.4	47.7 ± 2.4	34.7 ± 1.3	32.6 ± 0.8	36.0 ± 1.2
Thymus	278 ± 15	210 ± 40	267 ± 19	242 ± 6	223 ± 11
Heart	442 ± 14	350 ± 10	423 ± 11	436 ± 10	322 ± 8
Kidney	1025 ± 9	840 ± 20	1121 ± 33	1239 ± 28	881 ± 21
Vascular lesions					
Heart					
% Incidence	75	0	33	63	0
% Severity	42	0	11	33	0
Kidney					
% Incidence	100	20	100	100	0
% Severity	50	7	37	54	0
Panarteritis†					
% Incidence	0	0	0	0	0
% Severity	0	0	0	0	0

* All weights given with standard error of the mean.
† Pancreatic and mesenteric.

remained normotensive. This was not related to fluid intake but may have been related to lithium retention. Animals receiving DCA and drinking distilled water became hypertensive, development in those with restricted intake was somewhat slower at first, but ultimately reached comparable elevations of blood pressure. Animals not receiving steroid remained normotensive (Fig. 3).

Organ Weights: Animals receiving DCA and *ad libitum* water had smaller adrenal glands than did control rats, but this was not the case in those with limited intake. The adrenal glands of hypertensive animals receiving LiCl and DCA were of normal weight; those from normotensive animals on the same regimen were enlarged. The weights were expressed as a percentage of body weight.

Hearts and kidneys of hypertensive animals were greatly enlarged as compared to those of nontreated control rats or normotensive animals receiving LiCl and DCA. The thymus weight did not vary among groups.

Vascular Lesions: There was no evidence of periarteritis in any of the animals, perhaps because this experiment was of shorter duration than the preceding one, with the consequence that hypertension was of lesser magnitude and shorter duration.

Nephrosclerotic lesions were present in all hypertensive animals regardless of the type of fluid ingested, and were also observed in the kidney of one animal ingesting DCA and LiCl in which elevated pressures had never been recorded. Severity did not appear to differ greatly between the three hypertensive groups.

Cardiac vascular lesions appeared to be more numerous and severe in hypertensive rats re-

ceiving LiCl or unlimited water intake than in those whose fluid had been restricted (Table II).

EXPERIMENT 3

Method: In this experiment female rats weighing 120 to 140 gm. were used. Group 1 consisted of eleven animals which were hypophysectomized, unilaterally nephrectomized and had two 30 mg. pellets of DCA implanted subcutaneously. Group 2 also contained eleven animals which were similarly hypophysectomized, but uninephrectomy and implantation of two 30 mg. pellets took place 8 days later to allow a period of postoperative pituitary, and hence adrenal, insufficiency. Group 3 consisted of seven animals whose hypophysis was incompletely removed and which were otherwise treated as in group 2. Group 4 consisted of eight animals with pituitary intact but subjected to uninephrectomy. All animals received a drinking solution containing 0.85 per cent NaCl and 5 per cent sucrose and a diet of Purina laboratory chow *ad libitum*.

Blood pressures were measured and assessed as in the previous experiments.

The DCA pellets were removed on the eighty-ninth day of the experiment and NaCl supplementation of the drinking water was discontinued on the one hundred forty-fifth day. The animals were killed with ether on the one hundred eighty-first day.

Results: Hypertension developed in animals treated with DCA. This was most severe in the group in which the pituitary had not been entirely removed. There was no difference in response between groups 1 and 2. Hypertension also developed during the experiment in half of the intact group receiving NaCl supplementation without steroid treatment.

Removal of steroid was followed by a slight reduction, but not to normotensive levels, in blood pressure which was most evident in the incompletely hypophysectomized animals. This was followed by a gradual increase in blood pressure. Withdrawal of NaCl supplement did not significantly affect the severity of hypertension, either in hypophysectomized animals with metacorticoid hypertension or in the intact rats which had become hypertensive on the high NaCl intake. The blood pressure findings are given in Figure 4.

At autopsy no remnants of pituitary tissue were found in hypophysectomized animals, which, taken together with the lack of growth and development of the coarse guard hairs in the pelage which is thought to be an even more sensitive index of residual pituitary activity,[13] indicates that complete removal of the pituitary was achieved.

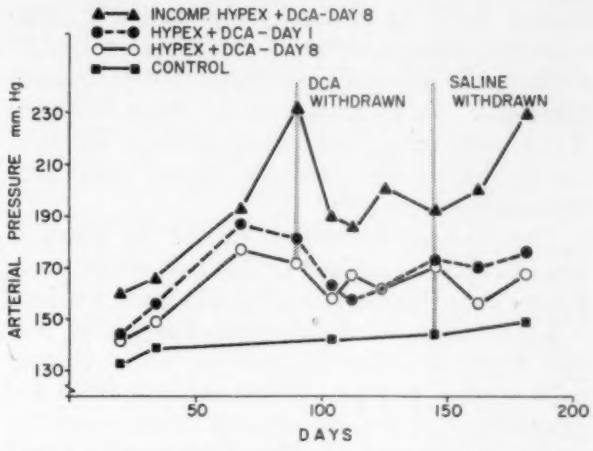

FIG. 4. Group average systolic pressure of groups of rats. Incompletely hypophysectomized and completely hypophysectomized groups were treated with DCA and NaCl, intact controls only with NaCl. Neither withdrawal of hormone nor of saline drinking fluid abolished hypertension in animals which became hypertensive through treatment.

COMMENTS

The results of the experiments on the effects of lithium chloride would indicate that the salt is capable of preventing the induction of hypertension by DCA when its toxic effects are sufficient to inhibit growth. When growth is not inhibited hypertensive cardiovascular disease develops as severely as in animals which consume either a like concentration of NaCl solution or distilled water.

The first experiment clearly indicated that DCA does not lead to increased ingestion of lithium-containing fluid. Despite ingestion of small quantities of electrolyte and volumes of solution, hypertensive cardiovascular disease was as severe as in DCA-treated animals which consumed several times as much NaCl solution. From this it may be inferred that the volume of fluid consumed, although great in animals on NaCl, had little effect on the steroid-induced hypertensive disease, and that the polyuria so evident in rats receiving DCA and NaCl is largely the result of the polydipsia and should not to be ascribed to renal pathology.

One might also suppose that Li was even more effective than Na in sensitizing to DCA effects. However, the second experiment clearly revealed that distilled water was just as effective as LiCl solution. It would seem, then, since it is known that DCA fails to cause hypertensive cardiovascular disease in rats on a sodium-free diet,[8] that the sodium in the commercial ration was sufficient at the hormone

dosage used to induce hypertensive cardiovascular disease, and that additional salt, either LiCl or NaCl, was essentially noncontributory. It is known that whereas added NaCl potentiates DCA effect at low hormone dosage it does not necessarily do so when large amounts are given.[3]

The adrenal involution caused by DCA in animals receiving NaCl or distilled water is not apparent in animals receiving DCA and LiCl.

Experiments in the hypophysectomized animal clearly demonstrate that not only corticoid hypertension but also a true metacorticoid hypertension can develop in such animals, treated with DCA and NaCl. The effects upon organ weight and vascular pathology are given elsewhere.[14] Thus, it appears that metacorticoid hypertension is not only independent of high NaCl intake but also of the hormones of the pituitary gland and those endocrine glands which are completely controlled thereby. The experiment provides no basis for the belief that metacorticoid hypertension might be due to steroid-induced adrenal hypofunction, the vascular system being thereby sensitized to normal corticoid levels resumed when steroid is withdrawn.[15] However, the possible role of aldosterone, the secretion of which may be largely independent of ACTH, remains to be elucidated.

Hypertension also developed in many animals not treated with steroid but receiving a high NaCl intake. This was not reversed by withdrawal of NaCl supplement. Hypertension here cannot be called metacorticoid, inasmuch as it was not induced by hormone treatment. Like metacorticoid hypertension, however, once established it persists after the evocative stimulus is withdrawn. The term metanatric hypertension might well be applied to this disorder.

Summary

Rats treated with DCA and drinking a solution of LiCl had hypertensive cardiovascular disease of a severity as great or greater than that in animals receiving DCA and NaCl solution, although they consumed only a third to a quarter as much electrolyte and solution. A second experiment showed that LiCl sometimes caused stunting of growth in smaller DCA-treated animals. These failed to become hypertensive, whereas those which grew did. At the dosage used, hypertensive cardiovascular disease caused by DCA was equally severe when no NaCl was added to the diet.

Hypertension following treatment with DCA and NaCl developed in hypophysectomized rats. The disorder developed in many intact rats on the same NaCl regimen which were not treated with steroid. Neither withdrawal of DCA and NaCl in the first instance, nor of NaCl alone in the second, led to normalization of blood pressure. It is concluded that metacorticoid hypertension can develop in the hypophysectomized rat, and that a sustained hypertension following prolonged NaCl excess develops in the intact rat. In each case withdrawal of sodium excess was without effect on the hypertensive state.

References

1. Selye, H., Hall, C. E. and Rowley, E. M. Malignant hypertension produced by treatment with desoxycorticosterone and sodium chloride. *Canad. M. A. J.*, 49: 88, 1943.
2. Selye, H. and Hall, C. E. Pathologic changes induced in various species by overdosage with desoxycorticosterone. *Arch. Path.*, 36: 19, 1943.
3. Green, D. M., Coleman, D. H. and McCabe, M. Mechanisms of desoxycorticosterone action. II. Relation of sodium chloride intake to fluid exchange, pressor effects and survival. *Am. J. Physiol.*, 154: 465, 1948.
4. Friedman, S. M., Friedman, C. L. and Polley, J. R. Potentiation of hypertensive effects of DCA by various sodium salts. *Am. J. Physiol.*, 153: 226, 1948.
5. Sapirstein, L. A., Brandt, W. L. and Drury, D. R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water. *Proc. Soc. Exper. Biol. & Med.*, 48: 505, 1950.
6. Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H. Hypertension edema and renal failure produced in the rat by high salt diet. *Am. J. Physiol.*, 171: 750, 1952.
7. Koletsky, S. Hypertensive vascular disease produced by salt. *Lab. Invest.*, 7: 377, 1958.
8. Selye, H., Stone, H., Timiras, P. S. and Schaffenburg, C. Influence of sodium chloride upon the actions of desoxycorticosterone acetate. *Am. Heart J.*, 37: 1009, 1949.
9. Fregly, M. J. Specificity of the sodium chloride appetite of adrenalectomized rats; substitution of lithium chloride for sodium chloride. *Am. J. Physiol.*, 195: 645, 1958.
10. Duliere, W. Le lithium dans le liquide de perfusion du coeur de grenouille. *Compte rend Soc. Biol.*, 97: 193, 1927.
11. Radomsky, J. L., Fuyat, H. N., Nelson, A. A. and Smith, P. K. Toxicity and effects on electrolyte excretion of lithium chloride administered to dogs. *Fed. Proc.*, 10: 310, 1950.
12. Hall C. E. Hall, O. and Rennels, E. G. Mineralocorticoid hypertensive cardiovascular disease induced in hypophysectomized rats. *Circulation Res.*, 8: 336, 1960.

13. RENNELS, E. G. and CALLAHAN, W. P. The hormonal basis for maturation of hair in the albino rat. *Anat. Rec.*, 135: 21, 1959.
14. HALL, C. E., RENNELS, E. G. and HALL, O. Metacorticoid hypertension in the hypophysectomized rat. *Lab. Invest.*, 10: 572, 1961.
15. STURTEVANT, F. M. The biology of metacorticoid hypertension. *Ann. Int. Med.*, 49: 1281, 1958.

The Enhanced Hypertensogenic Effect of Sea Salt over Sodium Chloride*

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THE ROLE of ingested table salt (sodium chloride) in human hypertension has been subjected to extensive investigation in our laboratory.[1-9] Other investigators have used excessive salt intake to induce experimental hypertension in the chick,[10] the rabbit[11] and the rat.[12,13] In all of these studies interest centered primarily on the sodium ion.

Several years ago[14] we became interested in the possibility that the sodium effect might be potentiated by additional elements. This question arose on considering the historic role of this ancient food condiment and preservative, the purification of which has evolved differently, so that even today there are wide variations in the purity of sodium chloride used by various peoples. Further impetus to exploring the role of additional ions was obtained in 1958 from a study of hypertension among the Japanese in whom the disease is common,[7,15] average salt consumption is high,[15] and the salt, derived by processing sea water, is often relatively impure.[16]

The present paper deals with the question "are there elements which potentiate the hypertensogenic effect of sodium?" The answer is affirmative. It is based on chronic salt feeding experiments with rats, some of which were fed sodium chloride while the others were fed what was thought to be the most naturally diversified mixture of elements available, namely, sea salt.

EXPERIMENTAL METHODS

Details may be found in the original papers.[17,18]

Animals and Food: All animals were Sprague-Dawley female rats. "Sea salt colony I" consisted of thirty-seven animals, of which twenty-five were salt-fed and twelve were controls; "sea salt colony II" had seventy-six animals, of which twelve were controls. Animals were kept in air-conditioned rooms with from two to six animals per cage with free access to drinking (tap) water and food. Control animals received unmodified Ralston Purina fox chow pellets, which contained 0.50 to 0.75 per cent NaCl by analysis. The salt-fed animals received the same chow to which one of two supplementary sodium-containing salts was added by the manufacturer according to our specifications, so that the final concentration of NaCl approximated 8 per cent by weight.

In one diet (8 per cent NaCl food) the supplementary salt was sodium chloride: our analyses indicated an average of 8.1 per cent NaCl. The other diet ("sea-salt food") had 11.6 per cent "sea-salt" added, an amount which had been calculated to give a final sodium concentration equal to that in the 8 per cent food; our analyses, however, showed this food to contain an average of 7.3 per cent NaCl. The manufacturer of this special sea salt† stated that it was obtained by evaporating sea water and drying at an air temperature of 1100°F. A comparison of the composition from data obtained by analysis at Brookhaven with that received from the manufacturer is summarized in Table I. No significant differences are apparent between the two analyses for the ions present in larger concentrations; however, differences were found among some of the others: strontium, copper, lithium, manganese, molybdenum, nickel, zirconium, silicon and tin were in significantly higher concentrations according to the Brookhaven analysis whereas boron, aluminum and fluorine were significantly lower than the corresponding analyses supplied by the manufacturer.

Regimens: The twenty-five salt-fed members of "sea salt colony I" received the unmodified chow from weaning to the age of $2^1/_2$ months when they were started on the food containing sea-salt. This was continued throughout the ensuing 14 months when eighteen salt-fed animals remained alive. Sea salt colony II was started 11 months after sea salt colony I when it had become evident that the sea salt feeding regimen not only was hypertensogenic but that it probably was more so than sodium chloride. Of

† We are indebted to the Trace Elements Corporation, Houston, for sufficient sea salt ("Admiral Brand Trace Element Sea Salt") to initiate these experiments.

* From the Medical Research Center, Brookhaven National Laboratory, Upton, New York. This work was supported by the United States Atomic Energy Commission.

TABLE 1
Analysis of Sea Salt

Constituent	Analysis by Supplier* (parts per million)	Analysis by Ourselves (parts per million)
Chlorine	50.5%	48.2%
Sodium	27.5%	28.1%
Magnesium	3.4%	3.03%
Carbon	2.7%	Not done
Sulfur	1.83%	Not done
Potassium	1.13%	1.0%
Calcium	0.86%	2.0%
Bromine	1,580	Not done
Strontium	220	1,000
Iron	100	100–200
Boron	97	±†
Aluminum	55	±
Fluorine	35	<5
Copper	20	500
Rubidium	5	±
Lithium	3	50
Iodine	1.5	<5
Barium	1.5	±
Nitrogen	0.3–20	±
Arsenic	0.3–0.6	±
Phosphorus	0.3	<5
Zinc	0.15	±
Manganese	0.03–0.03	50–100
Lead	0.11	±
Selenium	0.11	±
Cobalt	0.001–0.1	±
Cesium	0.06	±
Uranium	0.04	±
Molybdenum	0.013	100
Thorium	0.013	±
Silver	0.009	±
Vanadium	0.009	±
Lanthanum	0.009	±
Yttrium	0.009	±
Nickel	0.003	80–100
Scandium	0 0112	±
Mercury	0.0009	±
Gold	0.0002	±
Zirconium	Not reported	300
Silicon	Not reported	300
Tin	Not reported	300

* Approximate analysis supplied by Trace Elements Corp., Houston, Texas.

†± = None detected, or too low to measure by spectrographic analysis.

the sixty-four salt-fed members of this colony, thirty-six were fed the "sea-salt food" and twenty-eight the "8 per cent NaCl food" beginning at 1 month of age and thereafter for 13 months without change. At this time, twenty-seven sea-salt and nineteen NaCl-fed animals remained alive.

Food Consumption and Weights: This was measured in from six to twenty animals from each group for 3 to 30 consecutive days (most commonly about twenty animals for 4 successive days); in order to maximize variation, different cages of animals on the same regimen were studied from month to month. The weight of powdered pellets, offered in special cups, consumed during a 24 hour interval constituted the measurement. This was expressed as grams per rat per day.

All animals were weighed at the time blood pressure measurements were taken, usually at monthly intervals.

Blood Pressure: Measurement and values. The method of Friedman and Freed[19] was used with the modifications described.[17] The graphs in this paper which include control mean (and standard deviation) blood pressure data are based on our total experience over the last three years with nearly 100 female Sprague-Dawley rats on precisely the same control regimen. Successive monthly measurements on control animals up to 21 months of age have not shown systolic pressures consistently in excess of 130 mm. Hg. Therefore, we have regarded a systolic pressure regularly in excess of 140 mm. Hg as "hypertension," a value which generally exceeds the control mean by between one and two standard deviations. The value of 180 mm. Hg, which exceeds the control mean systolic pressure by almost five standard deviations, is a level which will drastically shorten life expectancy with the salt-feeding programs used in these studies.

Ordinarily blood pressures were recorded at monthly intervals. For technical reasons, no measurements were made on sea salt colony 1 from the fifth through the eighth month of age. Respiratory tract infections occasionally occurred in individual animals and under such circumstances, measurement of blood pressure was omitted for that month.

RESULTS

Sea Salt Colony I: The hypertensogenic potential of the sea-salt food is evident from Figure 1. From our previous experience the incidence and degree of hypertension seemed significantly greater in this group which had been fed sea-salt than with similar animals on NaCl feeding.

Sea Salt Colony II: The mean pressure of the group fed sea salt was consistently higher than that of the NaCl-fed group (Fig. 2). The difference became marked after 12 months on the experimental program, at which time the incidence of systolic blood pressures in excess of 180 mm. Hg (a level which will shorten life expectancy drastically) became particularly striking in the group on sea salt by comparison with the NaCl-fed group (Fig. 3). At this time from 30 to 40 per cent of the animals on sea salt had such pressures in contrast to only 5 to 10 per cent of those on NaCl. The increase in mean pressure of the group on sea salt at 12, 13 and 14 months as well as the increased prevalence of pressures above 180 mm. Hg at these times were all statistically significant (probability levels

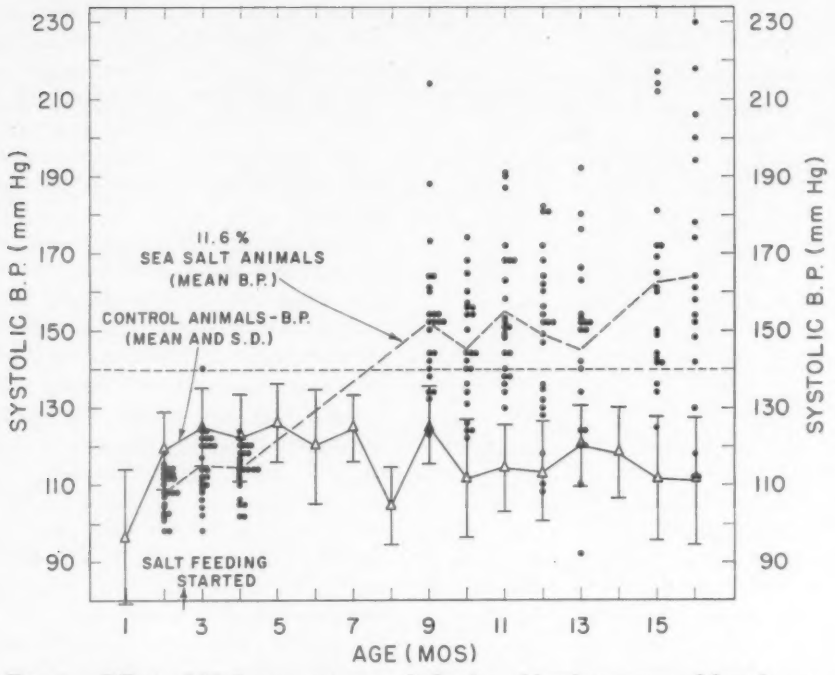

FIG. 1. Effect of 11.6 per cent sea salt food on blood pressure of female rats in "sea salt colony I." Dashed line through 140 mm. Hg indicates level at which "hypertension" is considered to begin. No measurements on these salt-fed animals were made from the fifth through the eighth months, for technical reasons.

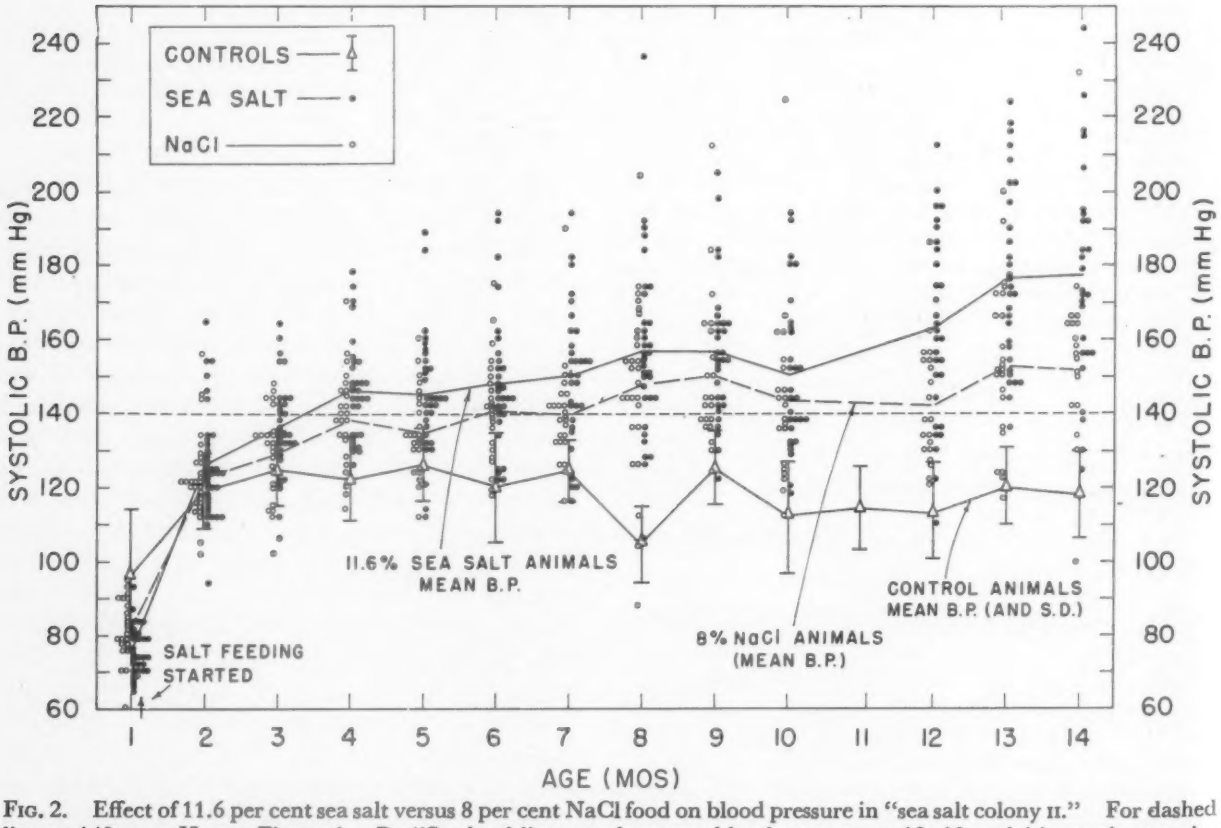

FIG. 2. Effect of 11.6 per cent sea salt versus 8 per cent NaCl food on blood pressure in "sea salt colony II." For dashed line at 140 mm. Hg see Figure 1. By "Student's" t test, the mean blood pressure at 12, 13 and 14 months was significantly higher in the group fed sea salt (at 12 months, $t = 3.16$, $p < .01$; at 13 months $t = 3.45$, $p < .01$; and at 14 months, $t = 2.49$, $p < .05 > .01$).

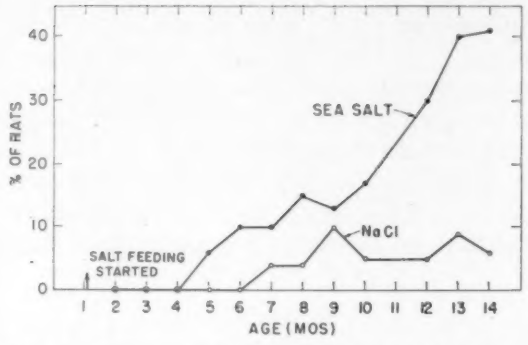

FIG. 3. Per cent of rats with systolic blood pressures in excess of 180 mm. Hg. Animals were given food containing either 11.6 per cent sea salt or 8 per cent NaCl. "Sea salt colony II" only. By the chi-square technic, the prevalence of this degree of hypertension was significantly greater in animals fed sea salt at 12, 13 and 14 months (at 12 months, $X^2 = 4.69$, $p < .05 > .01$; at 13 months, $X^2 = 6.68$, $p < .01$; and at 14 months, $X^2 = 7.96$, $p < .01$).

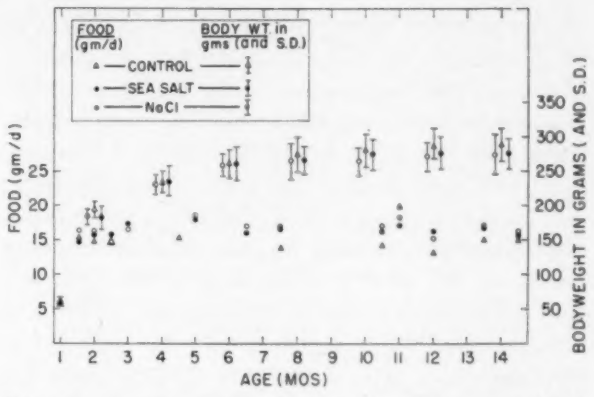

FIG. 4. Average daily food consumption and body weights of female rats on salt-feeding regimens compared with similar items for control animals.

ranged from less than 5 to less than 1 per cent).

Average Weights and Food Consumption: Excess consumption of sodium chloride by the animals on the sea salt regimen cannot be invoked to explain the findings. In Figure 4 the average daily food consumption and average weight of both salt-fed groups is summarized graphically from which it can be seen that no significant differences could be detected. Furthermore, since chemical analysis (see Experimental Methods) had indicated that the NaCl food contained slightly more sodium chloride than the food with sea salt added, then with food consumption equal in the two groups, the animals fed sea salt probably had a slightly lower average sodium chloride intake.

COMMENTS

The important role of sodium chloride consumption has been well documented in varieties of experimental hypertension associated with the administration of desoxycorticosterone acetate,[20] adrenal regeneration[21] and salt-feeding.[10–13] In general the evidence has been interpreted to indicate that sodium was primarily involved. The current work implicates ions in addition to sodium.

Selye[22] has described an experimental syndrome in rats associated with cardiac necrosis induced by desoxycorticosterone and various sodium salts. The degree of necrosis could be modified by the character of the anion. No data were presented to assess the possible effect of these anions on the hypertension presumably associated with this syndrome.

Trace Metals and Hypertension: The possible role of cations other than sodium in hypertension has been the subject of relatively infrequent investigation. Schroeder, Perry and their associates[23–27] found that except for the ganglionic blocking agents, all known antihypertensive agents had "an affinity for certain trace metals."[23] As a result, the hypotensive action was postulated to result from this metal-binding capacity. Measurements of urinary excretion and tissue concentrations of certain trace metals in hypertensive and normotensive persons suggested the possibility that trace metals might play a role in human disease, of which vanadium, cadmium, lead and manganese were the most suspect in human hypertension. Recently, Schroeder[27] analyzed mortality rates in the United States from cardiovascular diseases (including hypertension) relative to the hardness of water in various areas, and concluded that there was something "associated with the nature of public water supplies which affects adversely the course of degenerative cardiovascular disease in the United States."

Chlorides and Hypertension: Orbison, Christian and Peters[28,29] administered intraperitoneally to bilaterally nephrectomized dogs solutions of NaCl or modifications of Locke's solution and found that the complex cation-anion mixtures in the latter were more effective in causing hypertension as well as vascular disease than was the simple NaCl solution. Martini and Kaiser[30] and Kaiser[31] reported that both sodium and chloride were required for the pressor effect in clinical and experimental hypertension. The necessity for chloride in association with sodium has not been generally observed by ourselves or others.[30] The current work does not indicate which ion or ions may contribute to

the augmented hypertensive response observed in these rats. If one compares the composition of the sea salt used in our study with that of the Locke's solutions used by Orbison and associates, the two share the following ions (carbon, hydrogen and oxygen have been disregarded): Na, K, Ca, Mg, Cl and P. While there is more chloride than sodium in sea salt on a molar basis, we are aware of no data which indicate that chloride *per se* is hypertensogenic. Meneely and Ball[32] found that the addition of potassium (chloride) to diets decreased rather than increased the hypertensogenic effect of sodium chloride. In the syndrome which Selye reported,[22] the phosphate salt of sodium and some calcium salts enhanced the cardiac necrosis while magnesium (chloride) diminished it. It is possible that both phosphorus (as the phosphate) and calcium served to enhance the toxicity of sea salt in the current work.

While it would be intriguing to speculate on the possible role of the numerous trace ions in sea salt relative to the present findings, the paucity of facts negates its value. The four trace elements, which Schroeder suspected might be involved in human disease, cannot be ruled out as having played a role here since they were present in the sea salt. At the present juncture it seems fair to summarize by saying that from evidence now available, it is impossible to know whether these or other trace metals were involved. Insidious renal damage from some factor in sea salt cannot be eliminated as a cause of its enhanced hypertensogenic effect. It is unlikely that gross renal damage was brought about since blood urea nitrogen concentrations, determined at intervals, were with rare exceptions within normal limits. In addition, the continuing histologic and histochemical studies, which have been and are being made on these and other rats subjected to the same regimens, have not revealed significant differences between those animals which were fed sodium chloride and those consuming sea salt.[33]

Whatever the nature of the agent or the mechanism of its effect, sea salt apparently augments the hypertensogenic effect of sodium chloride. The data are insufficient to conclude that the findings have relevance to human hypertension although it seems permissible to speculate that they may.

Summary and Conclusion

For about 1 year rats were fed diets which contained an excess of either sea salt or sodium chloride. At the end of this period the hypertensive process in the group consuming sea salt was significantly more severe than in the group eating sodium chloride although the rats on sea salt probably ingested slightly less sodium chloride. The factor or factors involved in this incremental effect have not been identified.

Acknowledgment

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References

1. Dole, V. P., Dahl, L. K., Cotzias, G. C., Eder, H. A. and Krebs, M. E. Dietary treatment of hypertension. Clinical and metabolic studies of patients on the rice-fruit diet. *J. Clin. Invest.*, 29: 1189, 1950.
2. Dole, V. P., Dahl, L. K., Cotzias, G. C., Dziewiatkowski, D. D. and Harris, C. Dietary treatment of hypertension. II. Sodium depletion as related to the therapeutic effect. *J. Clin. Invest.*, 30: 584, 1951.
3. Dahl, L. K., Stall, B. G. and Cotzias, G. C. Metabolic effects of marked sodium restriction in hypertensive patients: changes in total exchangeable sodium and potassiun. *J. Clin. Invest.*, 33: 1397, 1954.
4. Dahl, L. K. and Love, R. A. Evidence for relationship between sodium (chloride) intake and human essential hypertension. *Arch. Int. Med.*, 94: 525, 1954.
5. Dahl, L. K., Stall, B. G. and Cotzias, G. C. Metabolic effects of marked sodium restriction in hypertensive patients. Skin electrolyte losses. *J. Clin. Invest.*, 34: 562, 1955.
6. Dahl, L. K. and Love, R. A. Etiological role of sodium chloride intake in essential hypertension in humans. *J.A.M.A.*, 164: 397, 1957.
7. Dahl, L. K. Salt intake, adrenocortical function and hypertension. *Nature, London*, 181: 989, 1958.
8. Dahl, L. K., Silver, L. and Christie, R. W. The role of salt in the fall of blood pressure accompanying reduction in obesity. *New England J. Med.*, 258: 1186, 1958.
9. Dahl, L. K., Silver, L., Christie, R. W. and Genest, J. Adrenocortical function after prolonged salt restriction in hypertension. *Nature, London*, 185: 110, 1960.
10. Lenel, R., Katz, L. N. and Rodbard, S. Arterial hypertension in the chicken. *Am. J. Physiol.*, 152: 557, 1948.
11. Fukuda, T. L'hypertension par le sel chez les lapins et ses relations avec la glande surrenals. *Union méd. Canada*, 80: 1278, 1951.
12. Sapirstein, L. D., Brandt, W. L. and Drury, D. R. The production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water. *Proc. Soc. Exper. Biol. & Med.*, 73: 82, 1950.

13. MENEELY, G. R., TUCKER, R. G., DARBY, W. J. and AUERBACH, S. H. Chronic sodium chloride toxicity in albino rat. II. Occurrence of hypertension and of a syndrome of edema and renal failure. *J. Exper. Med.*, 98: 71, 1953.
14. CHRISTIE, R. W. and DAHL, L. K. Dissimilarity in oxygen consumption between the thoracic and abdominal aorta in rats. *J. Exper. Med.*, 106: 357, 1957.
15. DAHL, L. K. Salt, fat and hypertension: the Japanese experience. *Nutrition Abstr. & Rev.*, 18: 97, 1960.
16. Outline of salt production in Japan. The Japan Monopoly Corp., Tokyo, 1958.
17. DAHL, L. K. Effects of chronic excess salt feeding. Elevation of plasma cholesterol in rats and dogs. *J. Exper. Med.*, 112: 635, 1960.
18. DAHL, L. K. and HEINE, M. Effects of chronic excess salt feeding. Enhanced hypertensogenic effect of sea salt over sodium chloride. *J. Exper. Med.*, 113:1067, 1961.
19. FRIEDMAN, M. and FREED, S. C. Microphonic manometer for the indirect determination of systolic blood pressure in the rat. *Proc. Soc. Exper. Biol. & Med.*, 70: 670, 1949.
20. SELYE, H., HALL, C. E. and ROWLEY, E. M. Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. *Canad. M. A. J.*, 49: 88, 1943.
21. SKELTON, F. E. Adrenal regeneration hypertension and factors influencing its development. *Arch. Int. Med.*, 98: 449, 1956.
22. SELYE, H. The Chemical Prevention of Cardiac Necroses, New York, 1958. p. 51. Ronald Press Co.
23. SCHROEDER, H. A. and PERRY, H. M. Antihypertensive effects of metal binding agents. *J. Lab. & Clin. Med.*, 46: 416, 1955.
24. SCHROEDER, H. A. and PERRY, H. M. Essential and abnormal trace metals in cardiovascular diseases. In: Proceedings of the Annual Meeting, Council for High Blood Pressure Research, 1955, vol. 4, p. 71. Am. Heart Assn., New York, 1956.
25. SCHROEDER, H. A. Mechanisms of Hypertension. With a Consideration of Atherosclerosis, p. 379. Springfield, Ill., 1957. Charles C Thomas.
26. PERRY, H. M. and PERRY, E. F. Normal concentrations of some trace metals in human urine: changes produced by ethylenediamine-tetra acetate. *J. Clin. Invest.*, 38: 1452, 1959.
27. SCHROEDER, H. A. Relation between mortality from cardiovascular disease and treated water supplies. *J.A.M.A.*, 172: 1902, 1960.
28. ORBISON, J. L., CHRISTIAN, C. L. and PETERS, E. Studies on experimental hypertension and cardiovascular disease. I. Method for the rapid production of malignant hypertension in bilaterally nephrectomized dogs. *Arch. Path.*, 54: 185, 1952.
29. ORBISON, J. L., PETERS, E. and CHRISTIAN, C. L. Studies on experimental hypertension and cardiovascular disease. II. The effect of fluid and electrolyte on bilaterally nephrectomized dogs. *Arch. Path.*, 61: 456, 1956.
30. MARTINI, P. and KAISER, K. The importance of sodium chloride and its ions in the production and the treatment of hypertension, p. 272. In: CIBA Foundation Symposium on Hypertension, Humoral and Neurogenic Factors. Ed. by Wolstеinholme, G. E. W. and Ameron, M. P. Boston, 1954. Little, Brown & Co.
31. KAISER, K. Essential hypertension and sodium chloride. *German M. Month.*, 4: 93, 1959.
32. MENEELY, G. R. and BALL, C. O. T. Experimental epidemiology of chronic sodium chloride toxicity and the protective effect of potassium chloride. *Am. J. Med.*, 25: 713, 1958.
33. DAHL, L. K., LIPPINCOTT, S. W. and CALVO, W. In press.

Effect of Potassium Nitrate Solutions on Blood Pressure of Rats*

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HYPERTENSION CAN be induced in rats by giving them diets rich in sodium chloride[1] or by giving them either isotonic[2] or hypertonic sodium chloride solutions[3,4] as their sole drinking fluid. Vascular disease[1,2] and cardiac hypertrophy[3] accompany the elevation of blood pressure. The rate of development of sodium chloride-induced hypertension appears to be increased by increasing the concentration of sodium chloride in the drinking water. Although these facts are well known, it cannot be stated with certainty that the sodium ion *per se* is responsible for the development of this type of hypertension. Therefore, it seemed worthwhile to test whether hypertension could be induced in rats by a salt other than NaCl, thereby testing the specificity of sodium chloride in production of hypertension. To this end, solutions of potassium nitrate have been used.

METHODS AND RESULTS

Two separate experiments were performed, both using male rats of the Holtzman strain. The similarities of experimental procedure in the two experiments are as follows: All rats were kept three to a cage in a room illuminated from 8 A.M. to 6 P.M. and maintained at a temperature of 26 ± 1°C. The food given was Purina laboratory checkers. Drinking fluids were given in bottles of the type described by Lazarow.[5] These consisted of nursing bottles with cast aluminum caps. Blood pressures were measured weekly using the microphonic manometer technic of Friedman and Freed, but without anesthesia.[6] The rats were accustomed to the procedure of blood pressure measurement for 1 week before the experiment began. During this period blood pressure was measured daily.

EXPERIMENT 1

Two groups of rats with five rats per group were used. At the end of a control period lasting 1 week, *group 1* was given 0.15 M. KNO_3 as the sole drinking fluid (Fig. 1). At the end of the third experimental week, 0.25 M. KNO_3 replaced 0.15 M. KNO_3. Treatment continued for 16 weeks. At the end of the nineteenth week, 0.30 M. KNO_3 was substituted for 0.25 M. This group was maintained on 0.30 M. KNO_3 until the experiment ended 16 weeks later. *Group 2* received tap water to drink during the first 10 experimental weeks. At the end of the tenth week, 0.15 M. KNO_3 solution replaced the water. At the end of the thirteenth week, 0.25 M. KNO_3 solution was given in place of 0.15 M. These rats received 0.25 M. KNO_3 solution until the end of the experiment. Concentrations of KNO_3 solution were increased gradually because previous experience with NaCl solutions had taught that rats given hypertonic concentrations often refuse to drink. This occurred less often when the concentration was increased gradually. Blood pressures were measured weekly for each group of rats.

Results: Mean systolic blood pressure of group 1 rose within a week after initiation of 0.15 M. KNO_3 as the sole drinking fluid. Blood pressure increased from a mean level of 145 to 155 mm. Hg. Blood pressure was maintained at this higher level for 19 weeks in spite of the fact that the concentration of KNO_3 was increased to 0.25 M. at the end of the third experimental week. Blood pressure rose to levels in the vicinity of 160 mm. Hg within 3 weeks after substituting 0.30 M. KNO_3 for 0.25 M. KNO_3. This latter blood pressure was maintained for the remainder of the experiment.

Mean systolic blood pressures of group 2 varied from 141 to 149 mm. Hg during the first 10 experimental weeks while water was the sole drinking fluid. After substituting 0.15 M. KNO_3 for water at the end of the tenth week, blood pressure rose to approximately 155 mm. Hg. Substitution of 0.25 M. KNO_3 for 0.15

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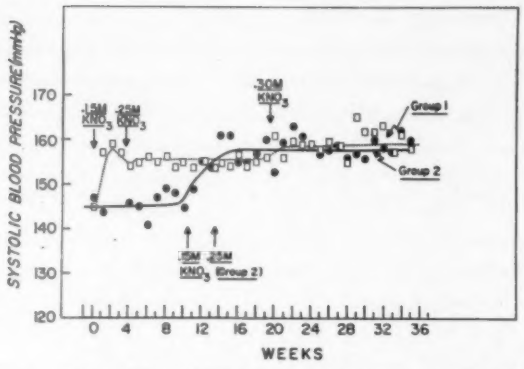

FIG. 1. The effect of KNO_3 solutions on systolic blood pressure of rats. *Group 1* (□) received 0.15 M. KNO_3 as the sole drinking fluid at time indicated as 0 on the abscissa. After 3 weeks, 0.25 M. KNO_3 solution was substituted for 0.15 M. At the end of the nineteenth week 0.3 M. KNO_3 was substituted for 0.25 M. This group continued to receive 0.3 M. KNO_3 until the end of the experiment. *Group 2* (●) received tap water to drink during the first 10 experimental weeks. At the end of the tenth week, 0.15 M. KNO_3 was substituted for tap water. Three weeks later 0.25 M. KNO_3 was substituted for 0.15 M. This group continued to receive 0.25 M. KNO_3 until the end of the experiment.

M. KNO_3 at the end of the thirteenth experimental week was accompanied by a further slight rise to a mean systolic level of approximately 157 mm. Hg. Blood pressure was maintained at this level for the remainder of the experiment.

EXPERIMENT 2

This experiment was performed to repeat and extend the observations made in experiment 1. A total of sixteen rats were used. At the end of a 2 week control period, eight of the rats were given only 0.15 M. KNO_3 solution to drink. The concentration of the KNO_3 solution was increased to 0.25 M. at the end of the fifth experimental week and to 0.30 M. at the end of the tenth experimental week. These rats were maintained on 0.30 M. KNO_3 for the duration of the 28 week experimental period. The remaining eight rats received tap water to drink throughout the experiment. All rats were given the drinking fluids and Purina laboratory checkers *ad libitum*. Blood pressures and body weights were measured weekly.

At the end of the twentieth week of the experiment the rats were placed in individual cages and given finely ground Purina laboratory checkers as food and their usual drinking fluid (either water or 0.30 M. KNO_3 solution). Fluid containers were the same as those used in experiment 1. Food containers have been described in detail in a publication dealing specifically with them.[7] After allowing the rats 4 days to accustom themselves to their new environment, individual food and fluid intakes were measured daily for 10 days. A sample of food was wet-ashed

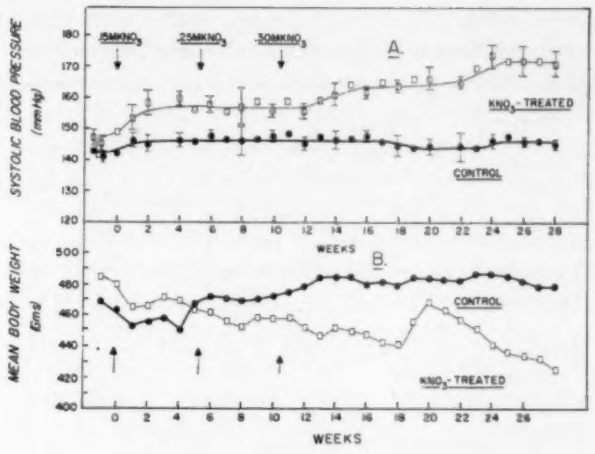

FIG. 2. A, the effect of KNO_3 solutions on systolic blood pressure of rats. *Treated rats* (□) were given 0.15 M. KNO_3 solution as sole drinking fluid at time indicated as 0 on the abscissa. After 5 weeks 0.25 M. KNO_3 solution was substituted for 0.15 M. Five weeks later 0.3 M. KNO_3 solution was substituted for 0.25 M. This group continued to receive 0.3 M. KNO_3 solution for the remainder of the experiment. *Control rats* (●) were given tap water to drink at all times during the experiment. ±1 standard error is set off at the means. B, *mean body weight* of KNO_3-treated (□) and control (●) rats throughout the experiment. Arrows indicate times when concentration of KNO_3 solution was changed.

with concentrated nitric acid and analyzed in duplicate for potassium by flame photometry. The potassium content of the food was found to be 206 mEq. per kg. The objective was to calculate the total potassium intake of the treated group.

Results: Some results of this experiment are shown in Figure 2. Systolic blood pressure of the KNO_3-treated group increased within 2 weeks after initiation of 0.15 M. KNO_3 as the sole drinking fluid (Fig. 2A). No further elevation of pressure was observed after treatment with 0.25 M. KNO_3. However, within 5 weeks after initiation of 0.30 M. KNO_3, blood pressures rose to levels of 160 mm. Hg and by the end of the experiment were 170 mm. Hg. Blood pressures of treated rats were significantly higher ($p < 0.01$) than control levels after the first experimental week. A single exception to this statement occurred during the eighth experimental week when the difference between means was not significant. We have no explanation for the greater variability of blood pressure which occurred at this time. Control rats maintained a relatively constant blood pressure throughout the experiment. Mean systolic blood pressure levels varied from 142 to 147 mm. Hg.

Mean body weight of the two groups of rats is

TABLE I

Ratio of Organ Weight to Body Weight (mg./100 gm. Body Weight) of Some Organs of the Rats in Experiment

Group	No. Rats	Mean Body Weight (gm.)	Mg./100 gm. Body Weight							
			Heart	Kidneys	Testis	Adrenal	Thyroid	Thymus	Seminal Vesicles	Prostate
Control	8	476	314.9 ± 6.0* (0.34†)	756.3 ± 22.4 (<0.01)	740.7 ± 30.1 (<0.01)	13.4 ± 1.2 (0.02)	8.7 ± 0.7 (0.14)	42.3 ± 3.1 (0.27)	141.8 ± 6.1 (0.95)	136.1 ± 9.5 (0.59)
KNO_3-treated	8	423	330.0 ± 13.9	966.2 ± 37.2	908.0 ± 41.8	20.0 ± 2.1	10.0 ± 0.5	50.6 ± 6.4	142.5 ± 9.0	126.7 ± 13.9

* ±1 standard error of mean.
† Probability value.

shown in Figure 2B. Body weight of control rats increased slightly after an initial fall. Mean body weight at the end of the experiment was about 10 gm. greater than initial body weight. In contrast, body weight of the KNO_3-treated rats fell during the course of the experiment. Body weight increased during the nineteenth and twentieth week but decreased thereafter to reach a level at the end of the experiment approximately 60 gm. below initial body weight.

The food intakes of the two groups of rats measured during the twenty-first week of the experiment were: 4.1 ± 0.3 (S.E.) gm. per 100 gm. body weight per day for control rats and 4.2 ± 0.2 gm. per 100 gm. body weight per day for KNO_3-treated rats. The difference between means is not significant ($P = 0.87$). The fluid intakes were: 10.4 ± 0.4 (S.E.) ml. per 100 gm. body weight per day for the control rats drinking water and 8.4 ± 0.3 ml. per 100 gm. body weight per day for the rats drinking 0.3 M. KNO_3. The difference between these means is significant ($p < 0.01$). The latter rats were ingesting 3.4 mEq. K per 100 gm. body weight per day; control rats ingested 0.84 mEq. per 100 gm. body weight per day. The treated rats ingested approximately four times as much potassium as did the control rats.

Organ Weights: At the end of the experiment all rats were killed by ether inhalation and organs, including heart, kidneys, testis, adrenals, thyroid, thymus, seminal vesicle and prostate, were removed, blotted on filter paper and weighed on a torsion balance.

Table I shows the weights of various organs of control and KNO_3-treated rats removed at autopsy. Ratios of kidney weight to body weight, testis weight to body weight and adrenal weight to body weight were increased significantly ($p < 0.01$) by treatment with KNO_3. The other organs of treated rats, including heart, thyroid, thymus, seminal vesicles and prostate, were not significantly changed from control values.

Statistical analyses of the data were performed using the Student "t" test for the 95 per cent confidence limit.[8]

COMMENTS

These studies represent preliminary observations on the physiologic effects of KNO_3 solutions administered to rats in their drinking water. Systolic blood pressures of rats drinking this salt solution became elevated within 2 weeks after treatment began. The maximal elevation of blood pressure occurred when 0.3 M. KNO_3 solution was given, although administration of isotonic KNO_3 solution also elevated blood pressure to a modest degree in both experiments (Fig. 1 and 2A).

Role of Potassium: The total potassium intake during administration of 0.3 M. KNO_3 as the sole drinking fluid was fourfold greater than that of controls given tap water to drink. Total fluid intake of treated rats was 81 per cent of that of control subjects. The virtual intake concentration of potassium (total potassium/total fluid times 1,000) for treated rats was 405 mEq. per L. while that for control rats was 81 mEq. per L. Treated rats ingested potassium in a five-fold greater concentration than control rats. While it is only possible to speculate concerning the mechanism of blood pressure elevation by KNO_3, apparently the osmolar concentration ingested is a factor. Presumably this is a factor in the range of concentrations from 0.23 to 0.3 M. since this

represents the upper limit of concentrating ability of the kidneys for potassium, sodium and chloride ions in both rats and man.[9,10] It is noteworthy that maximal elevation of blood pressure also occurred when 0.3 M. NaCl was given as the sole drinking fluid in earlier studies.[11] A greater yield of hypertension may then be induced in rats when the virtual intake concentration of either sodium or potassium is near the limit of the kidney to concentrate these ions in the urine. Perhaps continued maximal work of the kidneys plays a role in the development of salt hypertension.

A complete explanation of "salt" hypertension must also take into account the possibility that specific ions contribute to the production of hypertension. It would be difficult otherwise to explain why isotonic solutions of NaCl and KNO_3 are able to elevate blood pressure and to produce vascular lesions.[2]

Role of Nitrate Ion: It is also possible to speculate that the nitrate ion contributes indirectly to the elevation of blood pressure. Hiatt[12] observed that intravenous administration of large doses of isotonic $NaNO_3$ over a period of 1 to 13 weeks was accompanied by lowered plasma chloride concentration, elevated plasma bicarbonate concentration, elevated blood pH and decreased plasma osmolarity in dogs on a low chloride diet. The conditions of the present experiment were not the same as those of Hiatt; therefore, it can only be supposed that similar effects occurred. If so, the contribution of this altered acid-base balance to the elevation of blood pressure will need to be evaluated.

Other Contributing Factors: Clues to other factors that may contribute to elevation of blood pressure in KNO_3-treated rats are found in Table 1. An increase in the ratio of organ to body weight of kidney, testis and adrenal were observed in KNO_3-treated rats (Table 1). The increased kidney weight apparently reflects the *increased osmotic work to which the kidney was subjected* and is similar in degree (30 per cent increase) to that observed when the same concentration (0.3 M.) of NaCl is given to rats.[11]

The ratio of testis weight to body weight of treated rats increased 29 per cent above that of control rats. The same percentage increase in testis weight ratio was observed in rats given the same concentration of NaCl solution as their sole drinking fluid.[11] It seems unlikely that this increase in weight resulted from an increase in tissue water content since all tissues of the treated rats did not increase in weight (Table 1). The increased testicular weight is not accompanied by increased testosterone secretion as assessed by increase of weight in the seminal vesicle and prostate gland. Weights of these organs of treated rats were not different from control rats (Table 1). The increased testicular weight may reflect *increased secretion of gonadotrophic hormones* (*FSH*) by the anterior pituitary gland. Whatever the mechanism involved in its increase in size, we are left with the interesting question: Does the increase in testicular size play a role in the development of salt hypertension?

The increased ratio of adrenal weight to body weight of treated rats reflects *increased secretion of adrenocorticotrophic hormone* (*ACTH*) by the pituitary gland. Presumably, this arose as a result of undefined "stress" associated with the requirement to ingest a hypertonic KNO_3 solution. The thymus glands of treated rats did not show the decrease which characteristically accompanies an increase in glucocorticoid output. This lack of effect could be attributed to the fact that such a response is more difficult to observe in older rats in whom the thymus is already small. Under the conditions of this experiment one might expect maximal sodium-retaining activity to be manifest by the adrenal gland with consequent *increase in aldosterone secretion* accompanying the increased urinary sodium loss brought about by the nitrate ion.[13] We cannot state at present whether the adrenal cortex plays a role in the elevation of blood pressure under these conditions. The answer to this must await further study.

The ratio of heart weight to body weight of treated rats was larger than that of control rats but the difference between means was not significant ($p = 0.34$). Thus, the elevation of systolic blood pressure of the treated rats was not accompanied by a significant cardiac hypertrophy. In this single respect, treatment with hypertonic KNO_3 differs from treatment with hypertonic NaCl. Further studies are in progress to confirm this finding and to probe its significance.

Toxic Side Effects: Administration of KNO_3 appeared to be accompanied by minimal toxic side effects. A gradual weight loss occurred but the rats continued to eat and to keep themselves clean. Greene and Hiatt[14] also reported that there was no evidence of a severe toxicity in dogs given $NaNO_3$. Their dogs became ano-

rexic only after blood chloride levels had dropped to 65 per cent of normal.

Perhaps the concentration, time of administration, specific ion, renal concentrating ability and changes in acid-base balance all contribute to the elevation of blood pressure of salt-treated rats. The possibility of endocrine involvement further complicates the problem. Elucidation of the physiologic mechanisms by which KNO_3 elevates blood pressure must await further detailed study.

Summary

Administration of KNO_3 solutions to rats as their sole drinking fluid was accompanied by an elevation of systolic blood pressure. The maximal elevation of blood pressure occurred when the rats were ingesting 0.3 M. KNO_3 solution, although even an isotonic solution elevated blood pressure to a modest degree. Treatment was accompanied by a gradual loss of body weight. Ratios of organ weight to body weight of kidneys, testis and adrenals were increased by treatment with KNO_3 while organ weight ratios of heart, seminal vesicles, prostate, thyroid and thymus were not affected. A similarity exists between the physiologic responses of rats treated with the same concentrations of NaCl and KNO_3.

Acknowledgment

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References

1. Meneely, G. R., Tucker, R. G., Darby, W. J. and Auerbach, S. H. Chronic sodium chloride toxicity; hypertension, renal and vascular lesions. *Ann. Int. Med.*, 39; 991, 1953.
2. Koletsky, S. Hypertensive vascular disease produced by salt. *Lab. Invest.*, 7: 377, 1958.
3. Sapirstein, L. A., Brandt, W. L. and Drury, D. R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water. *Proc. Soc. Exper. Biol. & Med.*, 73: 82, 1950.
4. Fregly, M. J. Prevention of salt hypertension by propylthiouracil treatment in rat. *Proc. Soc. Exper. Biol. & Med.*, 102: 299, 1959.
5. Lazarow, A. Design and construction of metabolism cages. *Methods Med. Res.*, 6: 215, 1954.
6. Friedman, M. and Freed, S. C. Microphonic manometer for indirect determination of systolic blood pressure in the rat. *Proc. Soc. Exper. Biol. & Med.*, 70: 670, 1949.
7. Fregly, M. J. A simple and accurate feeding device for rats. *J. Appl. Physiol.*, 15: 539, 1960.
8. Fisher, R. A. Statistical Methods for Research Workers, ed. 10, p. 114. New York, 1948. Hafner.
9. Jacobson, H. N. and Kellogg, R. H. Isotonic NaCl diuresis in rats, antidiuresis and chloruresis produced by posterior pituitary extracts. *Am. J. Physiol.*, 184: 376, 1956.
10. Plough, I. C. and Baker, E. M. Maximum physiological concentration of sodium in human urine. *J. Appl. Physiol.*, 14: 1036, 1959.
11. Fregly, M. J. Production of hypertension in adrenalectomized rats given hypertonic salt solution to drink. *Endocrinology*, 66: 240, 1960.
12. Hiatt, E. P. Extreme hypochloremia in dogs induced by nitrate administration. *Am. J. Physiol.*, 129: 597, 1940.
13. Greene, I. and Hiatt, E. P. Renal excretion of nitrate and its effect on excretion of sodium and chloride. *Am. J. Physiol.*, 180: 179, 1955.
14. Greene, I. and Hiatt, E. P. Behavior of the nitrate ion in the dog. *Am. J. Physiol.*, 176: 463, 1954.

The Role of Potassium and Its Relation to Sodium in the Regulation of Blood Pressure*

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A great amount of evidence has been offered to indicate that sodium has a profound effect on inducing elevated blood pressure levels. Other cations have been implicated in this regard, but it is only relatively recently that data have appeared to suggest that potassium may be a significant factor. Investigations from this Institute over a number of years have indicated not only that potassium is directly responsible for increasing blood pressure, but also that sodium, under certain conditions, may have a depressing effect.

Initially, Rosenman and I fed rats synthetic diets containing varying amounts of sodium and potassium. To our surprise, in rats ingesting a diet rigidly restricted in potassiun marked and prolonged hypotension developed. This response was not obtained in rats fed a low sodium diet. As a matter of fact, when rats were fed a diet low in both sodium and potassium, blood pressure levels were not lowered. It would appear, therefore, that a decrease in dietary sodium protects against the blood pressure depression induced by potassium deprivation.

Naturally, it occurred to us that the hypotension of potassium depletion might be a nonspecific effect due to nutritional causes. However, the injection of KCl solutions into such rats promptly elevated the blood pressure to normal levels, which would indicate the specificity of potassium in this response.

An even greater lowering of blood pressure was observed when hypertensive animals were fed a potassium-free diet. Renal hypertensive rats became normotensive after several weeks on this diet. In such animals, blood pressures were promptly restored to hypertensive levels following replacement of potassium either by injection or in their drinking fluid.[1] Similarly, rats made hypertensive by DCA administration were fed a low potassium diet and they, too, had a depression of blood pressure. Incidentally, these rats were made hypertensive without the need of extra sodium chloride by using a method previously described by us.[2]

Mechanisms of Blood Pressure Lowering Effect of Potassium Deprivation

Adrenal Insufficiency: In search for a possible mechanism to explain the blood pressure depressing effect of potassium deprivation, we considered the possibility that this condition induced a suppression of adrenal steroid production. To test this hypothesis, ACTH and cortisone were administered to normal and hypertensive rats whose blood pressures were lowered by the dietary procedure. Both ACTH and cortisone induced a restoration to normotensive and hypertensive levels, respectively. These results suggested that an adrenal insufficiency could account for blood pressure depression. However, this theory was abandoned after an analysis of adrenal vein blood of potassium deficient rats failed to show any diminution of hydrocortisone or corticosterone content.

Loss of Arterial Tone: It was then postulated that potassium deprivation lowered blood pressure by removing potassium from the arterial wall, following which the smooth muscle lost its normal ability to contract, and this caused a loss of arterial tone. This deduction was considered reasonable since it had been previously observed that organs with smooth muscle, such as the bladder and intestine, are markedly distended in potassium deficient animals. This idea was tested by measuring the blood pressure response of potassium deficient rats to the intravenous administration of pressor agents such as norepinephrine and angiotensin. Our results demonstrated that such a response was approximately

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TABLE I

Effect of Nephrectomy and Ureteral Ligation on Electrolytes and Blood Pressure of Normal and Hypertensive Rats

Type of Rat	Average Original B.P. (mm. Hg)	Aorta*		Myocardium		Skeletal Muscle		Change in Blood Pressure (average) (mm. Hg)
		Na (mEq.-/kg.)	K (mEq.-/kg.)	Na (mEq.-/kg.)	K (mEq.-/kg.)	Na (mEq.-/kg.)	K (mEq.-/kg.)	
Normal	116	273	111	172	317	105	394	...
Normal, nephrectomy	112	236	100	168	289	126	385	−12
Normal, ureteral tie	108	238	104	167	294	128	392	−6
Hypertensive	186	280	131	161	294	100	379	...
Hypertensive, nephrectomy	192	266	110	167	298	127	408	−70
Hypertensive, ureteral tie	184	270	126	177	296	124	413	−12

* Fat-free dry weight.

half that obtained in normal rats. This suggested that potassium depletion weakened the contractility of arterial smooth muscle, a result not unexpected since potassium is an essential ingredient in the chemical process of muscle contraction.

More convincing evidence of this possible mechanism was made available through the investigations of Tobian and his associates.[3] They found a significant increase in the potassium content of the aorta of rats made hypertensive by a number of methods. They also reported an increased sodium content of this tissue. We were able to confirm the presence of an increased aortic potassium content but not that of sodium in renal hypertensive rats.[4] These findings were considered by us to support the hypothesis that potassium was directly involved in increasing arterial tone, thus enhancing the peripheral resistance.

Blood Pressure and Sodium-Potassium Ratio

Potassium-Sodium Ratio in Aorta: Since an altered renal function is a necessary or supplementary condition for most of the methods used for experimental hypertension, we were interested in observing the effect of nephrectomy on the aortic electrolytes. It was found that in renal hypertensive rats, nephrectomy but not ureteral ligation caused a marked drop in aortic potassium content in association with a fall in blood pressure to normotensive levels.[5] It was concluded that the ischemic kidney secreted a substance responsible for the elevated aortic potassium content as well as the increase in blood pressure (Table I).

Further investigation revealed a correlation between blood pressure levels and potassium concentration in the aorta. When normal and hypertensive rats were fed a low potassium diet, the fall in blood pressure to hypotensive and normotensive levels, respectively, was associated with an equivalent decrease in the potassium content of the aorta (Table II). Since the sodium content of this tissue remained at a constant level, it follows that the blood pressure levels varied inversely with the sodium-potassium ratio.[6]

Manipulation of blood pressure levels substantiated this relationship. Normal and renal hypertensive rats, whose blood pressures were lowered through potassium deprivation, were injected with cortisone and the blood pressures restored to previous levels. In the renal ligated rats, the aortic potassium content rose to the original high level, resulting in a diminution of the sodium-potassium ratio. In the normal rats,

TABLE II

Electrolyte Composition of Aortas of Renal Hypertensive Rats on Normal and Low K Diets

Type of Rat	Blood Pressure (mm. Hg)	Serum		Aorta*	
		K (mEq.-/L.)	Na (mEq.-/L.)	K (mEq.-/kg.)	Na (mEq.-/kg.)
Normal	114	5.2	146	111	273
Hypertensive	171	4.9	143	131	280
Hypertensive on low K diet	129	2.9	146	110	268
Normal on low K diet	82	2.8	144	94	263

* Fat-free dry weight.

TABLE III
Effect of Cortisone on Normal and Hypertensive Rats Fed a Low K Diet

Type of Rat	Aorta		
	Blood Pressure (mm. Hg)	K (mEq./kg.)	Na (mEq./kg.)
K-deficient	82	92	263
After cortisone	106	98	225
Hypertensive K-deficient	129	110	268
After cortisone	174	127	263

cortisone did not alter the lowered aortic potassium content, but caused a significant lowering of the aortic sodium content, similarly resulting in a smaller sodium-potassium ratio (Table III). In this manner, we have demonstrated that the shift in the sodium-potassium ratio in the aorta is in the opposite direction to the blood pressure change.

Sodium-Potassium Ratio in Myocardium: Recently, St. George and I reported that low blood pressure levels of potassium depletion are associated with a high sodium-potassium ratio in the myocardium.[7] In such rats with hypotension, this ratio is elevated mainly through a significant increase in myocardial sodium content, and only a slight decrease in potassium, in contrast to the aorta where the low potassium and normal sodium content also elevates this ratio. The administration of several adrenal steroids induced changes in the myocardial electrolytic pattern as well as blood pressure. Cortisone and prednisone induced a loss of sodium with restoration of blood pressure. Alpha-fluorohydrocortisone induced a loss of both sodium and potassium (no change in ratio) and no effect on blood pressure. DCA administration increased myocardial sodium and decreased the potassium content in association with a failure to restore blood pressure levels (Table IV). A similar high sodium-potassium ratio in the myocardium is found in clinical and experimental congestive failure. It is most interesting that relief of this condition is often obtained by anti-inflammatory steroid therapy.

Increased Aorta Sodium Content and Blood Pressure Depression: In still another condition, we were able to demonstrate the inverse correlation between the sodium-potassium ratio in the aorta and blood pressure level. As is well known, adrenalectomy reduces the blood pressure level of hypertensive animals, except in special situations. In our experience, renal hypertensive rats became normotensive following removal of both adrenals and maintenance on 0.9 per cent saline drinking fluid. Analyses of the aortas revealed that the potassium content remained at the original elevated values. However, the sodium content increased appreciably in these animals, resulting in a high sodium-potassium ratio.[8] The administration of prednisone, which restored the blood pressure to hypertensive levels, reduced the sodium content of the aorta so that the cation ratio returned to the original low values (Table V). These findings may possibly explain the so-called "permissive" action of the adrenal cortex in the maintenance of hypertension.

At this point, it would seem appropriate to offer a tentative explanation of the blood pressure depressing effect of an increased aortic sodium content. If one is permitted to assume that a

TABLE IV
Effect of Adrenal Steroids on Blood and Myocardial Electrolytes in Hypotensive Rats

Description of Rats	Original B. P. (mm. Hg)	B. P. Response (mm. Hg)	Serum		Myocardium	
			K (mEq./L.)	Na (mEq./L.)	K (mEq./kg.)	Na (mEq./kg.)
Normal control	114	112	5.5	144	317	172
Low K	82	80	3.6	141	303	216
Low K + cortisone	80	106	3.8	140	296	174
Normal + cortisone*	116	122	5.4	145	323	171
Low K + prednisone	84	108	3.5	146	301	173
Low K + 9a-fluorohydrocortisone	78	82	3.7	143	273	193
Low K + DCA	82	76	2.8	140	264	246

* Normal rats injected with prednisone, 9a-fluorohydrocortisone and DCA had similar values.

TABLE V

Effect of Adrenalectomy on Aorta Electrolytes in Hypertensive Rats

Type of Rat	Adrenalectomized Aorta			Control Aorta		
	K	Na	B.P.	K	Na	B.P.
Normal	107	259	104	111	273	112
Hypertensive	138	304	128	133	269	186
Hypertensive + cortisone	140	258	178	137	263	192

relative increase in tissue sodium signifies hydration, there may be justification in concluding that with the increase in cellular water the contractile elements become relatively diluted. This dilution might well interfere with the force of smooth muscle contraction and thus diminish arterial tone. This interpretation of "waterlogging" is opposed diametrically to that offered by other investigators who suggest that this effect induces increased peripheral resistance though narrowing of the lumen.

COMMENTS

There are numerous reports which are not in harmony with our concept of the role of potassium and the influence of the sodium-potassium ratio of vascular tissue on blood pressure regulation. Neither is it our intention to imply that the blood pressure can be calculated from the sodium-potassium ratio of the aorta. However, under any given experimental condition in which a shift in sodium-potassium ratio is induced, we are quite certain that we can predict the direction of change in the blood pressure level. It would appear, therefore, that the sodium-potassium ratio of vascular tissue has a considerable effect on circulatory dynamics.

SUMMARY

Results of our investigations suggest that potassium has a dynamic role in the regulation of blood pressure, as evidenced by the positive correlation between arterial content of potassium and the level of blood pressure. This relationship is influenced, however, by the content of sodium in arterial tissue. Thus, a relative excess of sodium depresses blood pressure, possibly through hydration of the arterial smooth muscle, the resulting dilution of contractile elements diminishing arterial tone. This explanation could account for our findings that the sodium-potassium ratio of arterial tissue uniformly shifts in opposite direction to the change in blood pressure level.

REFERENCES

1. FREED, S. C., ROSENMAN, R. H. and FRIEDMAN, M. The relationship of potassium in the regulation of blood pressure. *Ann. New York Acad. Sci.*, 56: 637, 1953.
2. ROSENMAN, R. H., FREED, S. C. and FRIEDMAN, M. Effect of DCA upon the blood pressure of rats fed varied dietary intakes of potassium and sodium. *J. Clin. Endocrinol.*, 14: 661, 1954.
3. TOBIAN, L. and BINION, J. Artery wall electrolytes in renal and DCA hypertension. *J. Clin. Invest.*, 23: 1407, 1954.
4. FREED, S. C., ST. GEORGE, S. and ROSENMAN, R. H. Arterial wall potassium in renal hypertensive rats. *Circulation Res.*, 7: 219, 1959.
5. FREED, S. C. and ST. GEORGE, S. Effect of nephrectomy on aorta electrolytes in hypertensive rats. *Proc. Soc. Exper. Biol. & Med.*, 106: 35, 1961.
6. FREED, S. C., ST. GEORGE, S. and ROSENMAN, R. H. Aorta electrolytes of hypertensive potassium-deficient rats. *Am. J. Physiol.*, 195: 445, 1958.
7. FREED, S. C. and ST. GEORGE, S. Myocardial sodium and potassium in relation to blood pressure. *Am. J. Physiol.*, 197: 214, 1959.
8. FREED, S. and ST. GEORGE, S. Effect of adrenalectomy on aorta electrolytes. In preparation.

Autoregulation of Blood Flow in Peripheral Vascular Beds*

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AUTOREGULATION of blood flow refers to the phenomenon whereby changes in perfusing pressure of a tissue or organ produce relatively small changes in blood flow. This autoregulation of blood flow is accomplished in the tissue or organ and requires neither neural nor vascular connections to the rest of the animal. It is characterized by an increase in resistance to blood flow after an increase in perfusion pressure and a decrease in resistance to blood flow after a decrease in perfusion pressure. This is in direct opposition to passive vascular beds in which an increase in perfusion pressure produces a decrease in vascular resistance presumably as a result of passive distention of the resistance vessels. Under these conditions a decrease in perfusion pressure produces an increase in resistance to blood flow because of elastic recoil which produces a passive decrease in mean resistance vessel radius.

The phenomenon was first described for the hind limb by Bayliss[1] in 1902 but has been largely ignored until fairly recently. Much attention has been given to autoregulation of blood flow in the kidney. With one exception the investigators have observed the phenomenon and have been concerned with its cause. The exception is the work of Langston, Guyton and Gillespie[2] who have reported that autoregulation is an artifact which appears only in a damaged kidney. Other areas have received less attention. It has been reported for brain and the gut and in the hind limb of the cat and dog, particularly by Folkow.[3,4]

The experiments presented herein are from studies on single groups of skeletal muscle. They indicate that autoregulation of blood flow is a regular and characteristic property of skeletal muscle and approaches in degree that described for the kidney. A detailed description of the transient and steady state pressure-flow relationships will be presented in an attempt to point out some of the possible mechanisms involved.

METHODS

The studies were performed on dogs of from 7 to 41 kg. of body weight anesthetized with pentobarbital, chloralose, urethane or diallylbarbituric acid intravenously or intraperitoneally with additional doses if needed. The animals were warmed by radiant heat to keep rectal temperature at approximately 37°C. Coagulation was prevented with heparin or polyanhydromannuronic acid sulphate (Manuronate®). Two muscle groups were used in these studies, the gracilis and the gastrocnemius-plantaris muscles.

The gracilis preparation was pump-perfused after isolation of the arterial and venous circulations. Venous outflow was measured by a drop counter and recorded via an inverted ordinate writer. Two perfusion systems were used. In one the perfusion pressure was regulated and flow was the dependent variable. In the other blood was displaced by oil under high pressure producing a pulseless, constantly flowing perfusion. Perfusion pressure was the dependent variable measured.

The gastrocnemius-plantaris preparation was perfused after isolation of the blood supply by the animal's own blood pressure. The actual perfusion pressure of the muscle was regulated from zero to the animal's full blood pressure by a small Starling resistance bypass between the femoral artery and vein in the contralateral leg as shown in Figure 1. When the Starling resistance is connected to one pressure reservoir the other could be pre-set at any desired pressure. Turning the stopcock is all that was required to produce an instantaneous change in perfusion pressure of the muscle group. The per-

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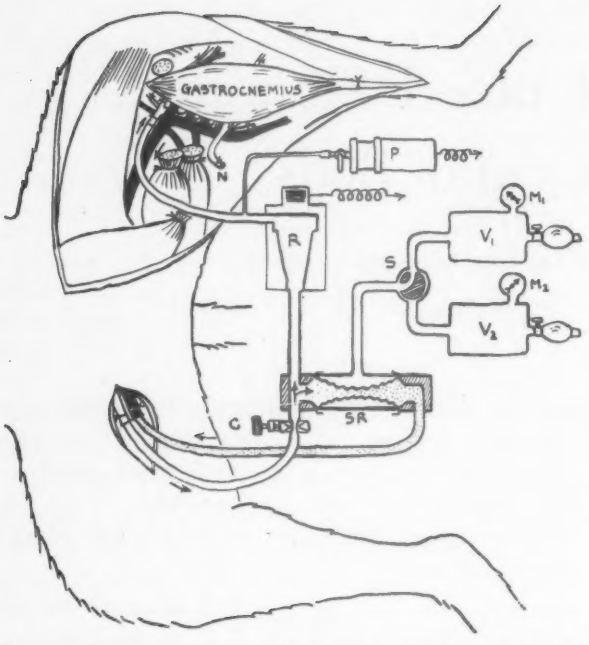

FIG. 1. Bypass apparatus for regulation of the perfusion pressure to the gastrocnemius-plantaris muscles *in situ*. SR is the Starling resistance connected between the femoral artery and vein of the right leg. C is a screw clamp. Leads V_1 and V_2 are the pressure reservoir bottles. S is the stopcock for connecting one or the other pressure bottle to the Starling resistance. R is a recording rotameter, and P is a pressure transducer. N is the sciatic nerve (cut in this preparation). FROM: Stainsby, W. N. and Renkin, E. M. Autoregulation of blood flow in resting skeletal muscle. *Am. J. Physiol.*, 201(1): 117, 1961.

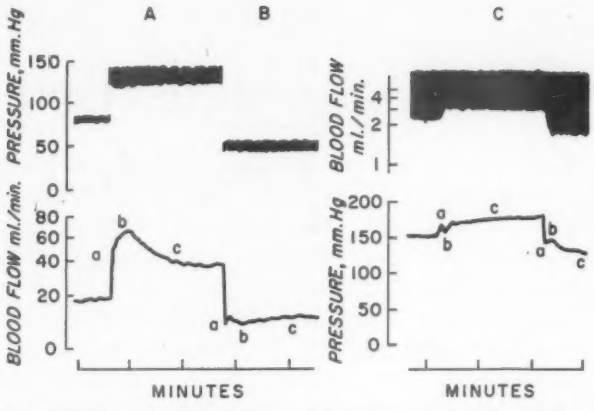

FIG. 2. Experimental records showing vascular reactions to sudden changes in pressure and flow. A, response to a sudden increase in mean perfusion pressure (Experiment H-12 gastrocnemius, 62 gm. *in situ* bypass perfusion). B, response to a sudden decrease in perfusion pressure. C, responses to sudden changes in blood flow (Experiment G-14, gracilis, 38.7 gm., constant flow pump perfusion). For full explanation see text. FROM: Stainsby, W. N. and Renkin, E. M. Autoregulation of blood flow in resting skeletal muscle. *Am. J. Physiol.*, 201(1): 117, 1961.

fusion pressure was measured by a Statham pressure transducer. The blood flow was measured by a rotameter.

RESULTS

The data to be presented were derived from approximately fifty experiments equally divided among the three muscle preparations: the *in situ* constant pressure perfusion, the pump-perfused constant pressure perfusion and the pump-perfused constant flow perfusion. All three preparations were studied innervated and acutely denervated. Although there were quantitative differences between one preparation and another even within each group, the qualitative relationships were similar.

Response to Sudden Changes in Perfusion Pressure or Flow: When the pressure of the blood perfusion in either skeletal muscle group was suddenly raised the blood flow followed the pattern exemplified in Figure 2A. First there was a sudden rise in blood flow (a), followed by a more gradual rise (b), which was in turn followed by a gradual fall toward the original flow level (c). The converse occurred when the pressure was suddenly lowered (Fig. 2B). The entire cycle required from 1 to 2 minutes for completion in resting muscle. Pressure changes as small as 10 mm. Hg in either direction were sufficient to produce detectable changes of the type shown. Completely analogous transient changes were observed in the muscles perfused by the constant flow apparatus (Fig. 2C). When the flow was suddenly increased, perfusion pressure rose quickly (a), fell transiently (b), and then rose to a higher, steady level (c). Small vascular responses were observed after changes in pressure or flow of short duration, 1 to 5 seconds. These observations are similar to those reported by other investigators who have studied autoregulation of blood flow.

These characteristic responses to changes in pressure or flow were present in all the self-perfused preparations and persisted until the experiments were terminated. Most of the pump-perfused muscles showed this vascular reactivity to pressure changes. Others lost their reactivity spontaneously after periods of time varying from a few minutes to 2 hours. Under these circumstances or when the vascular reactivity was deliberately abolished by the addition of chloral hydrate to the perfusion reservoir, 1 to 2 mg. per milliliter of blood, a sudden alteration of perfusion pressure or flow brought about a direct change of flow or pres-

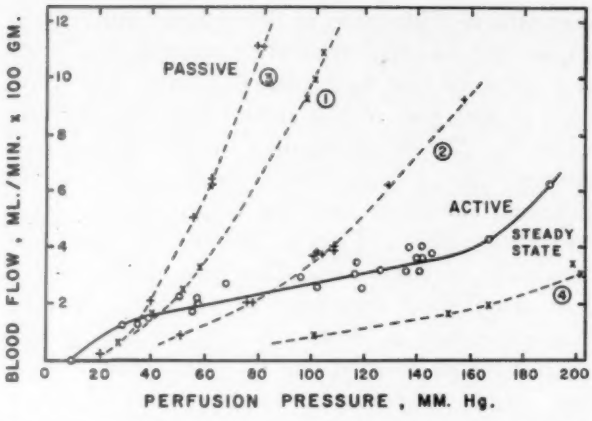

FIG. 3. Active and passive pressure-flow curves in a denervated gracilis muscle artificially perfused with blood. Experiment P-24, hematocrit 60 per cent and muscle weight 10.5 gm. Perfusion pressure was pulsatile, with pulse pressure about a third the mean. Steady state flows while the vascular bed was reactive to sudden changes in mean perfusion pressure (0.110 min. of perfusion) are indicated by open circles and the solid curve. The broken curve designated 1 was taken after spontaneous loss of vascular reactivity (150 to 175 minutes). The curve marked 2 was produced by the addition of 0.01 μgm. norepinephrine per milliliter blood (180 to 215 minutes); on return to blood with no norepinephrine added, the curve became almost identical to 1. Curve 3 was observed after addition of 2 mg. per milliliter chloral hydrate to the blood (370 to 288 minutes) and curve 4 on subsequent addition of 0.15 μgm. per milliliter norepinephrine (292 to 313 minutes). FROM: Stainsby, W. N. and Renkin, E. M. Autoregulation of blood flow in resting skeletal muscle. *Am. J. Physiol.*, 201(1): 117, 1961.

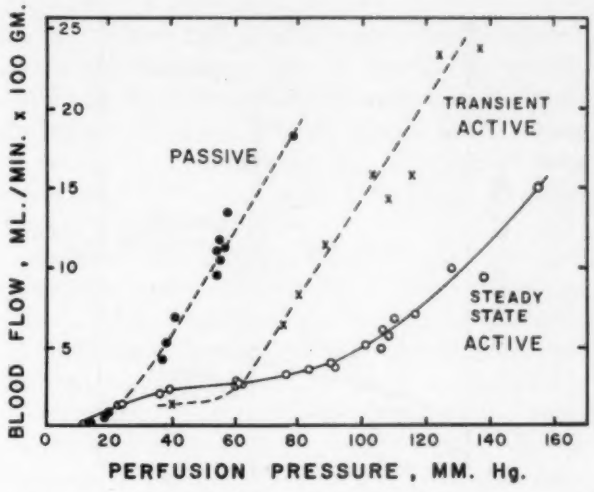

FIG. 4. Steady state and transient pressure-flow curves in a reactive vascular bed compared with a passive pressure flow curve. Experiment P-21, gracilis, 9.9 gm., denervated, artificially perfused with blood:hematocrit 44 per cent. The vascular bed was reactive for 185 minutes of perfusion. The open circles represent the steady state pressure-flow relation; the crosses, the maximum flow rates observed transiently on suddenly raising the perfusion pressure from 60 to 62 mm. Hg to the indicated values. (In one case, the minimum flow on lowering pressure is indicated.) Flow then fell from these maxima to the steady state level indicated by the circle directly beneath each cross. The fully dilated, passive pressure flow curve (closed circles) was obtained by addition of 1 mg. per milliliter chloral hydrate to the blood. Each point on it was reached directly on changing the perfusion pressure. FROM: Stainsby, W. N. and Renkin, E. M. Autoregulation of blood flow in resting skeletal muscle. *Am. J. Physiol.*, 201(1): 117, 1961.

sure to a new steady level. The pressure flow relations in these nonreactive preparations were as described before: an increase in perfusion pressure or flow was followed by a reduction in resistance to flow, and a decrease in perfusion pressure or flow was followed by an increase in resistance to blood flow.

Regulation of Blood Flow: In both the innervated and the acutely denervated preparations which show this vascular reactivity to pressure change, the steady state blood flow (end of phase c) changes relatively little over a wide range of perfusion pressures. This we have defined as autoregulation. A typical steady state pressure-flow curve is illustrated in Figure 3. Below 40 mm. Hg, the curve for this gracilis muscle is concave to the pressure axis probably due to the development of critical closure phenomena. Above 140 mm. Hg, the curve is convex to the pressure axis probably because the maximum contracting force of the vascular smooth muscle is exceeded and they begin to be distended by increasing pressure. In between these limits, the curve is relatively linear with some scattering of the points which is especially apparent in innervated muscles as a result of changing vasomotor nerve activity. Also shown is a series of passive pressure flow curves observed in the same preparation after spontaneous disappearance of the vascular response to pressure change. The different levels of vascular tone were produced by addition of norepinephrine, chloral hydrate, or both to the perfusing blood. It is evident that the autoregulated curve follows none of these. It is interesting to note that norepinephrine is very effective as a vasoconstrictor when vascular reactivity to pressure change is absent.

Relation of Transients to Autoregulation: As seen in Figure 2, the flow does not move immediately to its new steady state value after a sudden elevation of perfusion pressure, but goes through a cycle in which a large transient increase in flow is observed. Starting at one point of reference on the steady state curve and

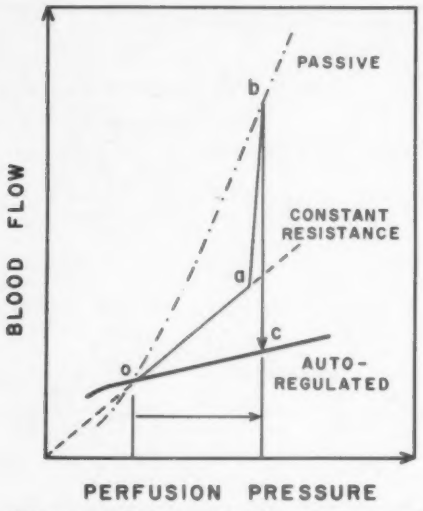

FIG. 5. Diagram of the mechanics of changes in blood flow following a sudden elevation of perfusion pressure in a reactive vascular bed. For explanation, see text. FROM: Stainsby, W. N. and Renkin, E. M. Autoregulation of blood flow in resting skeletal muscle. *Am. J. Physiol.*, 201(1): 117, 1961.

increasing the perfusion pressure by varied steps, we observed that the maximal transient flows fall along a straight line having a much steeper slope than the steady state curve (Fig. 4). The slope approaches that of the passive curve, which in the example illustrated, was produced by adding chloral hydrate to the blood reservoir. The same relationship between maximal transient flows and the passive pressure-flow relationship was observed when autoregulation disappeared spontaneously in other experiments. The position of the maximal transient curve is shifted along the pressure axis, according to its point of origin on the steady state curve. The maximal transient curve originating from zero pressure and flow is generally superimposed on the passive curve obtained from the same muscle group. Minimal transient flows observed on lowering perfusion pressure from a reference point on the steady state curve fell on a curve below and nearly parallel to the steady state curve. These relationships are very similar to those presented by Thurau and Kramer[5] and Waugh and Shanks[6] for the kidney, and by Johnson for the intestine.[7]

COMMENTS

Mechanics of the Transient Response: The successive events following a sudden rise in perfusion pressure may be described in a somewhat idealized fashion as follows: Assuming that a finite time is required to bring about measurable distention of the vessels, one would expect the vascular resistance immediately after the pressure rise to be unchanged. The flow rate at the end of the initial fast rise in flow (a in Fig. 2A) should lie on a straight line drawn through the pressure flow point prior to the pressure elevation and the origin of the pressure flow plot. This is illustrated diagrammatically in Figure 5. The flow rises along a line of constant resistance to point a. Having reached point a (Figs. 2A and 5) the vessels then distend toward elastic equilibrium with the raised internal pressure bringing about a further increase in flow (b in Figs. 2A and 5). The maximal transient flow should be on a curve determined by the purely passive distensibility of the vessels in their original state of tonus (Fig. 4). The third phase of the transient response consists of a return toward the original flow level. Since this occurs even though the increased internal pressure is maintained, we believe it must result from an active contraction of vascular smooth muscle. This contraction establishes the final steady state flow level (the end of phase c, Figs. 2A and 5) at the new pressure by increasing vascular resistance above that which existed at the low pressure. Complete separation of the successive events does not actually occur. For example, the passive changes in flow are somewhat diminished by the onset of contraction of smooth muscle and consequent increase in vascular resistance. The transient changes in flow following a sudden fall in perfusion pressure follow the same pattern in reverse (Fig. 2B). Similarly, the transient changes following a sudden alteration in flow can be explained by the same sequence of events.

Physiologic Mechanism Leading to Contraction of Smooth Muscle: Autoregulation of blood flow is the result of the third phase of the transient response, the contraction of the vascular smooth muscle. Over the years at least four different theories have appeared to explain autoregulation. The first to appear was proposed by Bayliss[1] who believed that the phenomenon was due to contraction of the smooth muscle as a direct response of the smooth muscle to stretch. The response begins and operates within the smooth muscles, hence the term myogenic was used. The second was proposed by Kinter and Pappenheimer[8] for the kidney who believed that the phenomenon resulted from changes in vascular resistance derived from red cell skimming. The skimming in combination with the

alinear hematocrit-viscosity relationship make this a tenable theory. The third theory, proposed for the kidney, states that autoregulation is the result of increased tissue pressure in the kidney. The fourth theory states that blood flow is regulated by a metabolically linked stimulus.

The easiest of these theories to eliminate is that concerning red cell skimming. Good autoregulation has been seen when perfusing with cell free perfusate.[6]

Waugh and Shanks[6] have also shown that autoregulation occurs more quickly than changes in tissue pressure in the kidney. As a result they believe the two phenomena are unrelated. The gut and skeletal muscle which lack capsules and are not observed to exhibit significant tissue pressure changes with alterations in blood flow in the autoregulated flow range, particularly when perfused with blood, would seem to be tissues in which the tissue pressure theory is even more untenable.

The myogenic theory of autoregulation is at present generally accepted and the response is in line with the general contraction of smooth muscle in response to stretch. This theory, with its positive feed-back whereby an increase in pressure provokes an increase in resistance to flow and hence a possible further increase in pressure and so on, would seem to be a very intriguing state of affairs to those interested in the genesis of hypertension.

However, the observation that vascular resistance increases after an increase in perfusing pressure rather than simply returning toward a fairly constant resistance, independent of pressure level, can only occur if the radius of the resistance vessels is reduced at higher pressure or that fewer vessels are open. In either case the radius and therefore the circumference of the vessels responsible for the increased resistance must be smaller at higher pressures, and direct extension of their muscular walls as required in the simplest interpretation of the myogenic hypothesis cannot be the stimulus for the sustained contraction.

If stretch of some part of the vascular wall is the stimulus for contraction of vascular smooth muscle, it must operate on a receptor which does not contract itself, but which in some manner transmits to the smooth muscles the stimulus to contract. This receptor may be located within the vascular smooth muscle in series with the muscle cells, or in another part of the vascular bed. If its location were distal to the resistance vessels concerned with the autoregulation response, it would be ideally suited for keeping pressure constant in the post-resistance vessels. As far as we know, there is no direct evidence for the location of such receptors in any particular part of the vascular bed, if they exist at all.

Folkow[9] has recently affirmed his view that arteriolar vasoconstriction is a direct myogenic effect. He explained the apparent paradox of maintained stretch stimulation of shortened smooth muscle cells in terms of a population of asynchronous, rhythmically contracting areas in the resistance vessels. If the stretch during relaxation determines the frequency of contraction, and hence the fraction of time a given arteriole is constricted, an increase in over-all vascular resistance should result from a higher internal pressure. This vasomotion which is so apparent in skin and mesentery is not readily apparent in muscle; however, aside from this, we can think of nothing definitely supporting or contradicting the view.

Metabolic Stimulus: The final possibility to be considered is that autoregulation of blood flow is maintained by a metabolic stimulus. It is well established that blood flow is varied in accordance with changes in metabolism of skeletal muscle as exemplified by active and reactive hyperemia. Either the smooth muscles themselves may be sensitive to the concentration in their environment of O_2, CO_2, H^+ or a more complex metabolic product, or they may be activated indirectly by receptor cells sensitive to such substances. All that is required is that the substance be consumed or produced in the tissue in proportion to its metabolism. The observation of vascular responses after pressure changes of only 2 to 3 seconds' duration seems to be evidence against the metabolically linked stimulus. It is hard to imagine a significant change in the concentration of a metabolite in so short a time (especially since blood flow seems relatively insensitive to experimental changes in concentrations of most metabolites). However, this observation does not definitely preclude such a mechanism.

The difficulty of explaining autoregulation of blood flow by a mechanism linked to tissue metabolism is brought out even more clearly in the case of the kidney in which the blood flow relative to metabolism is much higher (20×) than in skeletal muscle and yet the autoregulatory changes take place more quickly.

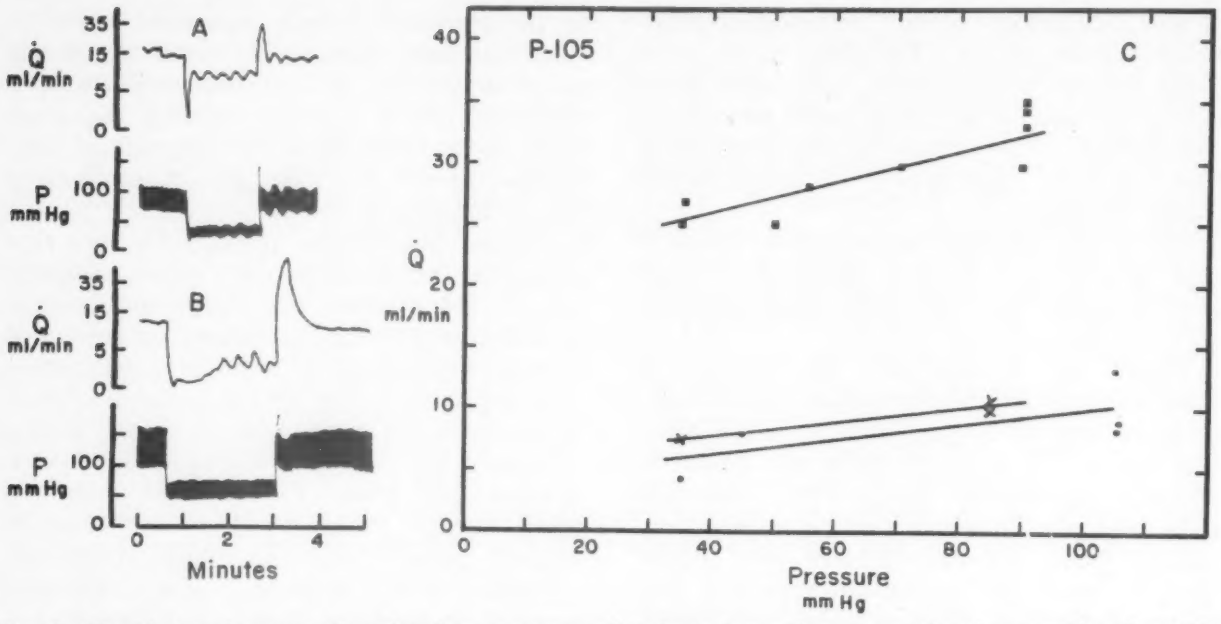

FIG. 6. Transient and pressure flow data from gastrocnemius-plantaris muscle group resting, innervated and acutely denervated, and during contractions, one per second. B is a pressure and flow record from Experiment P-102 resting innervated or denervated. A is the pressure flow record from the same experiment during muscular contractions. C shows the steady state pressure flow curves from a different experiment; ●—● = resting innervated, ×—× = resting acutely denervated, and ■—■ = during muscle contractions. P = pressure. Q = flow rate.

The easy way out, of course, is to say that the mechanism of autoregulation does not have to be the same in the two organs.

A thought that occurred to us was that if a metabolically linked stimulus were responsible for autoregulation of blood flow, one might expect that the range of blood flows within which autoregulation is observed would be altered by changing the level of metabolism. This possibility was put to test using the self-perfused preparation of the gastrocnemius-plantaris muscles. Autoregulation was studied with the preparation innervated, acutely denervated and then during continuous stimulation of the sciatic nerve with single shocks once per second. The stimulation increased oxygen uptake approximately sevenfold. The pressure-flow data from two of these experiments are presented in Figure 6. In Figure 6B are seen the transient cycles typical of resting muscle. Figure 6A shows the transient flow responses during stimulation of the same muscle. Good autoregulation is evident at a slightly higher blood flow, but the striking change is in the time required for completion of the transient cycle. Where resting muscle requires 1 to 2 minutes for completion of the transient cycle, the contracting muscle completes its cycle in less than 20 seconds. The steady state pressure flow curves on the right are from a different experiment, one in which the increase in blood flow during the contractions was larger. The degree of autoregulation during the contractions is essentially the same as when the muscle was at rest. One notes also the lack of difference between the innervated and denervated curves of the muscle at rest.

Bradykinin and Hyperemia: Active and reactive hyperemia have been proposed by Hilton and Lewis[10] to result from the production in the tissue of a vasodilator substance, bradykinin. This fairly complex polypeptide is produced in direct proportion to the metabolic rate of the tissue. Increased production of the substance during activity and resultant increased metabolism has been proposed as the cause of active hyperemia. Accumulation of the substance during periods of vascular occlusion produces reactive hyperemia. The kinetics of the transient responses at rest and during activity, as well as the change in the autoregulated flow level, can be accounted for on the basis of this hypothesis. A sudden rise in perfusion pressure produces an increase in blood flow and washes away the dilator which results in vasoconstriction. A sudden decrease in perfusion pressure produces a decrease in flow which results in an increase in concentration of the dilator substance and vasodilation. All the same explanations fit the responses to sudden

flow changes using the constant flow apparatus. At higher metabolic rates the substances are produced at a proportionately higher rate and this combined with a more uniform distribution of flow causes the more rapid transients and the higher level of autoregulated blood flow.

All this is hypothetical and may be an oversimplification. The metabolic link to autoregulation seems clear for muscle. How it may work in the kidney remains to be seen. One very interesting question that is left unanswered by this hypothesis is the source of the original vasoconstriction which is overridden by the metabolically linked dilator stimulus. In other words, why is resting blood flow as low as it is? The traditional source of vasoconstrictor tone, the nerves, seem to play a relatively unimportant role. Perhaps the basic vasomotor tone is myogenic. It is easier to say that circulating substances are the cause, but if so it would seem that the catecholamines are suspect, since passive vascular beds seem to respond well to injected catecholamines. Why should they cease to respond to those already present in the blood? Again this may be an oversimplification. Perhaps some other blood-born substance is responsible. Finding the answers to these questions may be pertinent to the genesis of hypertension. The answers will certainly have profound effects on concepts of regulation of peripheral circulation.

Summary

Blood flow through the vascular beds of innervated and acutely denervated gastrocnemius-plantaris and gracilis muscles of dogs was studied following sudden changes of perfusing pressure or blood flow. These vascular beds exhibited autoregulation of blood flow. When the muscle was contracting intermittently the degree of autoregulation was equal to that of resting muscle but at a higher level of blood flow. The level of blood flow which was autoregulated was relatively proportional to the metabolic rate. It appears that the autoregulation phenomenon is linked to the metabolism of the muscle.

References

1. Bayliss, W. M. On the local changes of the arterial wall to changes of internal pressure. *J. Physiol.*, 28: 220, 1902.
2. Langston, J. B., Guyton, A. C. and Gillespie, W. J., Jr. Autoregulation absent in normal kidney but present after renal damage. *Am. J. Physiol.*, 199: 495, 1960.
3. Folkow, B. A study of the factors influencing the tone of denervated blood vessels perfused at various pressures. *Acta physiol. Scandinav.*, 27: 99, 1952.
4. Folkow, B. Intravascular pressure as a factor regulating the tone of the small vessels. *Acta physiol. Scandinav.*, 17: 289, 1949.
5. Thurau, K. and Kramer, K. Die Reaktionsweise der glatten Muskulatur der Nierengefasse und Dehnungsreise und ihre bedeutung fur die Autoregulation des Nierenkreislaufes. *Arch. ges. Physiol.*, 268: 188, 1959.
6. Waugh, W. H. and Shanks, R. G. Cause of genuine autoregulation of renal circulation. *Circulation Res.*, 8: 871, 1960.
7. Johnson, P. C. Autoregulation of intestinal blood flow. *Am. J. Physiol.*, 199: 311, 1960.
8. Kinter, W. B. and Pappenheimer, J. R. Role of red blood corpuscles in regulation of renal blood flow and glomerular filtration rate. *Am. J. Physiol.*, 185: 349, 1956.
9. Folkow, B. Discussion in: Symposium on Central Nervous Control of Circulation. *Physiol. Rev.*, 40: 66, 1959.
10. Hilton, S. M. and Lewis, G. P. The relationship between glandular activity, bradykinin formation and functional vasodilatation in the submandibular salivary gland. *J. Physiol.*, 134: 471, 1956.

Effect of Dietary Sodium:Potassium Ratio on Body Content of Sodium and Potassium in Rats*

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THE TOXIC EFFECTS of increased dietary sodium chloride have been reported and include hypertension, renal damage and shortened life span.[1–3] In experiments using albino rats, increased dietary potassium afforded some protection against the toxicity of sodium chloride.[4] Rats fed high levels of both sodium and potassium chloride lived longer and had less severe hypertension than did rats on equivalent levels of sodium chloride without added potassium. Experimental hypertension in animals has frequently been associated with increased tissue content of sodium and we have reported significant increases in sodium space in rats fed increased levels of dietary sodium chloride.[5] In view of these findings it seemed possible that the protective action of increased dietary potassium against sodium chloride toxicity might be associated with changes in tissue concentrations of sodium and potassium. Exchangeable body sodium and potassium and tissue concentrations of these elements were measured in rats fed different amounts of sodium and potassium chloride.

The present investigation consisted of measurements of sodium space, exchangeable body sodium, exchangeable body potassium and tissue concentrations of sodium and potassium in rats receiving various levels of dietary sodium and potassium chloride. Increases in body sodium without measurable decreases in potassium content were observed in rats fed large amounts of sodium chloride. Rats fed these same amounts of sodium chloride with increased dietary potassium had normal amounts of body sodium but increased concentrations of potassium.

METHODS

Thirty day old male albino rats of the Sprague-Dawley strain were placed on the experimental diets and kept in a constant temperature room (27 ± 2°C.) with free access to distilled water. All animals received the same nutritionally complete purified basal diet, the composition of which has been described.[1] The only variable was the amount of NaCl and KCl; the concentrations which were fed are listed in Table 1. Sufficient K was added to diets high in NaCl to maintain a fairly constant Na:K ratio of approximately 1.† The control rats were fed 1.1 per cent NaCl because we have seen consistently better growth and more resistance to respiratory infection in rats fed this level rather than the usual 0.2 per cent NaCl. Each experimental group consisted of twenty rats. Systolic blood pressure was measured at monthly intervals by the cuff method of Kersten et al.[6]

1. *Measurement of Exchangeable Body Sodium:* After 8 months on the experimental diets, ten rats were selected from each dietary group and exchangeable body sodium [$(Na)_E$] was determined by the principle of isotope dilution. Each rat was injected intraperitoneally with 25 μc. of $Na^{24}Cl$ dissolved in 1 ml. saline; 5 hours later samples of blood were obtained from the tail. During the 5 hour equilibration period the rats were given access to water but not to food; all urine was collected in order to correct for urinary loss of radioactivity. Measurements of radioactivity were made using samples of both serum and urine with a scintillation well counter. Serum Na concentrations were determined using a Coleman flame photometer. Sodium space, expressed as per cent

† Na:K ratio as used here is based on relative rather than equivalent weights.

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TABLE I
Dietary Na and K

Diet	NaCl (%)	KCl (%)	Na:K Ratio
Low Na	0.2	0.66	0.2
Control	1.1	0.66	1.2
2% Na + K*	5.6	3.5	1.2
2% Na*	5.6	0.6	6.9
3% Na + K*	8.4	5.3	1.2
3% Na*	8.4	0.6	10.9
4% Na + K*	9.8	6.1	1.2
4% Na*	9.8	0.6	13.0

* These figures are approximations of the actual sodium content of the diet which are used to identify the various rations.

body weight, specific activity of serum and $(Na)_E$ expressed as milliequivalents per kilogram of body weight were calculated as follows:

$$\text{ml. Na space} = \frac{\text{cps. } Na^{24} \text{ injected} - \text{cps. } Na^{24} \text{ excreted}}{\text{cps. } Na^{24}/\text{ml. serum}}$$

$$\text{per cent Na space} = \frac{\text{ml. Na space}}{\text{gm. body weight}} \times 100$$

$$\text{Serum specific activity} = \frac{\text{cps. } Na^{24}/\text{L.}}{\text{mEq. Na/L.}}$$

$$(Na)_E \text{ mEq.} = \frac{\text{cps. } Na^{24} \text{ injected} - \text{cps. } Na^{24} \text{ excreted}}{\text{serum specific activity}}$$

The validity of the described method was established by preliminary experiments with animals from the stock colony. $(Na)_E$ was determined in three rats by the method of isotope dilution: The animals were killed, the entire carcass homogenized, an aliquot digested with nitric acid, and Na measured in the digest using the flame photometer. In the three rats $(Na)_E$ represented 87, 93 and 90 per cent of the total body Na as measured by chemical analysis of the carcass.

2. *Measurement of Exchangeable Body Potassium:* Rats from each of three dietary groups (control, 4 per cent Na and 4 per cent Na + K) were used for measurement of exchangeable body potassium $[(K)_E]$ after 12 months on the experimental rations. No animals were selected who appeared ill or were losing weight. Each rat was injected intraperitoneally with 100 μc. of K^{42} and 18 hours allowed for equilibration with body K. During this period the rats were given access to water but not to food. All urine was collected in order to correct for the amount of K^{42} lost by this route. Eighteen hours after injection the rats were anesthetized with urethane, the carotid artery cannulated and blood samples collected. Blood from the tail was not suitable for the measurement of the specific activity of K since it contained unusually high concentrations of K due to hemolysis and contamination with tissue fluid. After 5 ml. of blood was obtained, the rat was killed by removing the heart. Samples of ventricular muscle, skeletal muscle and liver were removed for determination of radioactivity and analysis of K content by flame photometry. One milliliter aliquots of blood serum were dried and counted with an end-window Geiger-Mueller tube. The urine, ventricular muscle, skeletal muscle and liver were counted with a scintillation well counter. Standard K^{42} solutions were then counted with both types of equipment to obtain a factor for converting beta counts to gamma counts. The K activity of serum was too low to be counted accurately in the well-type counter; urine and tissue samples could, however, be so counted. The scintillation well counter used for urine and tissue avoided the necessity of digestion and drying of samples before counting. K concentrations were measured in serum, urine and nitric acid digests of tissues with the flame photometer.

$(K)_E$ was calculated as follows:

$$\text{Serum specific activity} = \frac{\text{cps. } K^{42}/\text{L.}}{\text{mEq. K/L.}}$$

$$\text{mEq. } (K)_E = \frac{\text{cps. } K^{42} \text{ injected} - \text{cps. } K^{42} \text{ excreted}}{\text{serum specific activity}}$$

$(K)_E$ concentrations were calculated in terms of lean body weight since after 12 months on the diets the control animals were much fatter than the two experimental groups. Three rats from each group (control, 4 per cent Na, and 4 per cent Na + K) were killed for determination of fat content. After removing the skin and intestinal contents, the carcass of each animal was finely ground, and fat determined by the method of Lowry and Hastings.[7]

This method for measurement of $(K)_E$ in rats was compared with values obtained when total carcass K was estimated by flame photometry. The specific activities of serum and urine from four stock rats were determined and the two compared as representative body samples for calculation of $(K)_E$. Examination of urine collected at 6, 18, 21 and 24 hours after injection of K^{42} showed that the specific activity of the urine reached a constant value, indicating complete mixing, 18 hours after injection. The specific activity of the urine was about 20 per cent higher than that of serum. The individual values obtained for $(K)_E$ based on serum specific activity were 99, 111, 115 and 112 per cent of those obtained by analysis of carcass K. $(K)_E$ calculated from the specific activity of urine was 89, 80, 92 and 111 per cent of the values for total body K based on analysis of the carcass. The specific activity of serum samples was used for the determination of $(K)_E$ in these experiments. The concentrations of $(K)_E$ were then expressed as milliequivalents per kilogram of lean body weight.

3. *Measurement of Tissue Water Sodium and Potassium:* After 12 months on the experimental rations, eight rats from each of three dietary groups (control, 4 per cent Na and 4 per cent Na + K) were studied

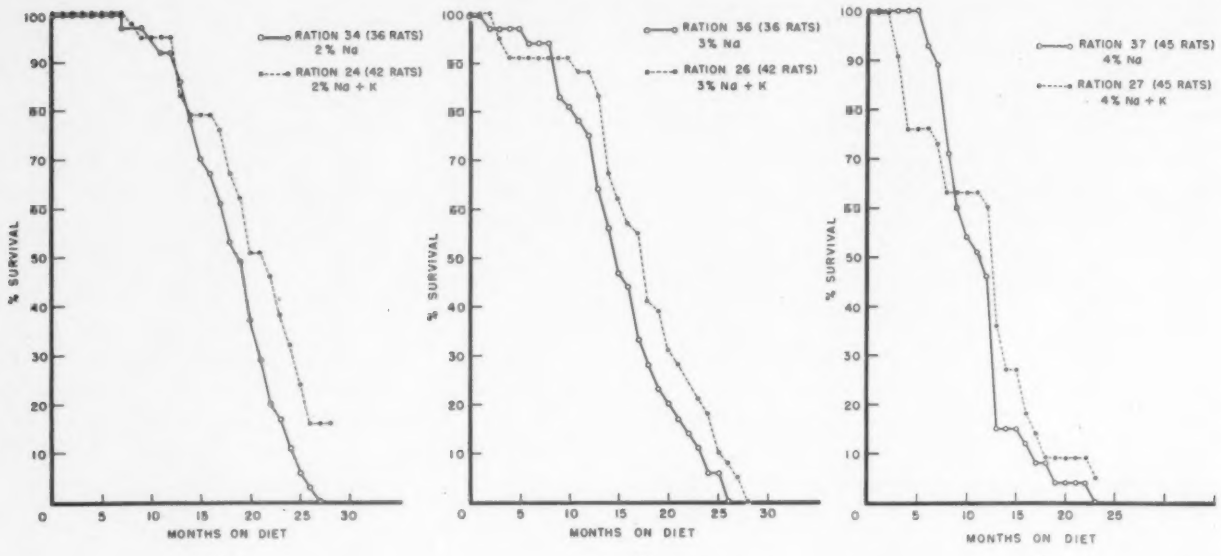

FIG. 1. A, survival of rats eating 2 per cent sodium with and without added potassium. B, survival of rats eating 3 per cent sodium with and without added potassium. C, survival of rats eating 4 per cent sodium with and without added potassium.

to determine tissue concentrations of water, Na and K. Weighed samples of ventricular muscle, skeletal muscle, liver and crushed bone were dried for 24 hours at 100°c., reweighed, digested with nitric acid and analyzed for Na and K. The concentrations in bone were expressed as milliquivalents per 100 grams of dry, fat-free bone. In preliminary experiments it was noted that the percentage fat in the tissue samples taken from the rats on the three experimental diets was less than 2 per cent so that ether extraction was omitted and the concentrations were expressed as milliequivalents per 100 grams dry tissue. Percentage water was calculated from the difference between the weight of fresh and dried tissue.

RESULTS

1. Effect of Added Dietary Potassium on Longevity and Blood Pressure: It has previously been reported that rats fed high levels of NaCl have a shortened life span[2,3] and that the survival time of these animals is lengthened if the KCl content of the diet is increased sufficiently to maintain a dietary Na:K ratio of 1.[4] This protective effect of K against chronic NaCl toxicity was confirmed in the present series of experiments. The results are shown in Figure 1. It will be noted that the survival of rats receiving 2 or 3 per cent dietary Na with added K was greater than those receiving high levels of Na without supplementary K. At the highest level of dietary Na (Fig. 1C) the addition of K appeared further to decrease survival during the early months of the experiment but after the eighth month, the survivors receiving increased K lived longer than those fed 4 per cent Na alone. Table II shows the average maximum blood pressure for a control group and those fed varying amounts of Na and KCl. The maximum blood pressure of rats fed high Na-high K diets was significantly lower than that of rats fed equivalent amounts of Na without added K. The hypertension associated with NaCl toxicity was not prevented but was somewhat reduced by feeding supplementary KCl.

2. Effect of Added Dietary Potassium on Sodium

TABLE II

Effect of Added Dietary KCl on Maximum Systolic Blood Pressure

Diet	No. of Rats	Blood Pressure		
		Maximum (mm. Hg)	Difference (mm. Hg)	"P" Value of Difference
Control	15	146 ± 1.80*	...	...
2% Na	20	164 ± 3.74		
2% Na + K	20	154 ± 1.31	10	<0.02
3% Na	19	181 ± 3.49		
3% Na + K	16	163 ± 1.50	18	<0.001
4% Na	20	186 ± 5.17		
4% Na + K	13	169 ± 4.79	17	<0.05

* Standard error of mean.

TABLE III
Effect of Added Dietary KCl on Na Space and $(Na)_E$

Diet	Serum Na (mEq./L.)	Na Space (% body weight)	$(Na)_E$ (mEq./kg. body weight)
Low Na	143 ± 0.71*	24.2 ± 0.52	34.4 ± 0.81
Control	141 ± 1.12	23.2 ± 0.56	32.7 ± 0.88
2% Na	140 ± 2.1	24.7 ± 0.65	34.5 ± 0.82
2% Na + K	141 ± 0.81	24.7 ± 0.38	34.7 ± 0.58
3% Na	145 ± 1.00	27.0 ± 0.53	39.2 ± 0.82
3% Na + K	146 ± 1.25	25.2 ± 0.40	36.7 ± 0.72
4% Na	143 ± 0.99	29.6 ± 0.72	42.2 ± 0.98
4% Na + K	138 ± 1.12	25.6 ± 0.43	35.4 ± 0.58

* Standard error of the mean.

Space and Exchangeable Body Sodium: The results summarized in Table III are the mean values for Na space and $(Na)_E$ in eight groups of rats. There were no significant differences in Na space or $(Na)_E$ in the first four dietary groups receiving low Na, control, 2 per cent Na and 2 per cent Na + K. Rats fed 3 or 4 per cent Na without increased K had significantly higher Na space and $(Na)_E$ than the control animals. These differences were statistically significant, having probability values of less than 0.001. Rats fed either 3 or 4 per cent Na also had significantly higher Na space and $(Na)_E$ than did those fed the same level of Na with added K ($p < 0.02$ for 3 per cent Na vs. 3 per cent Na + K; $p < 0.001$ for 4 per cent Na vs. 4 per cent Na + K). Despite excessive dietary Na intakes for 8 months, rats receiving high levels of dietary K did not show significantly greater Na spaces or $(Na)_E$ than their controls. Under these experimental conditions a Na intake in excess of 2 per cent resulted in retention of Na but this retention was prevented when the dietary KCl was raised sufficiently to maintain a Na:K ratio of 1.

3. Effect of Added Dietary Potassium on Exchangeable Body Potassium: $(Na)_E$ was determined on eight groups of experimental animals receiving various levels of Na and K. The largest differences occurred in body Na of three groups: control rats, 4 per cent Na and 4 per cent Na + K. Therefore, $(K)_E$ was measured in these same three groups in order to determine whether there was a reciprocal relationship between body Na and K. By the time the Na measurements were completed the rats had been on the experimental rations for 8 months, whereas body K was measured after 12 months on the diets.

Average $(K)_E$ of control rats, rats fed 4 per cent Na, and animals fed 4 per cent Na + K are shown in Table IV. Concentrations were calculated as milliequivalents per kilogram lean body weight to adjust for differences in body composition. The difference between the K content of control animals as contrasted with the 4 per cent Na fed rats was not statistically significant. The group receiving 4 per cent Na with added dietary K had significantly more $(K)_E$ than the control group ($p < 0.001$). The group receiving the 4 per cent Na diet with supplementary K had more body K than those fed 4 per cent Na without added K ($p < 0.01$). The animals on high Na diets had increases in $(Na)_E$ and decreases in $(K)_E$ as compared with those on the same level of dietary Na but with sufficient K added to restore the ratio to the control level of 1. When the two experimental groups are compared with the control group those on increased dietary Na had increased $(Na)_E$ whereas the group fed increased dietary Na + K had more $(K)_E$ than the control group.

TABLE IV
Effect of Added Dietary KCl on $(K)_E$

Diet	No. of Rats	Serum K (mEq./L.)	Fat (% body weight)	$(K)_E$ (mEq./kg. lean body weight)
Control	7	5.35 ± 0.40*	36.0	90.7 ± 1.95
4% Na	6	4.88 ± 0.30	26.4	94.6 ± 1.85
4% Na + K	5	5.16 ± 0.40	23.9	107.6 ± 2.36

* Standard error of the mean.

The values reported here for $(K)_E$ were based on the specific activity of serum but at the time these experiments were done tissue samples were also taken. These tissues were counted and later analyzed for K content. Specific activity of the tissue samples was calculated and compared with that of plasma as shown in Table V. The specific activities of heart,

TABLE V
K^{42} Specific Activity Relative to Plasma

Area	Diet		
	Control	4% Na	4% Na + K
Heart	1.22	1.06	1.12
Muscle	1.15	1.09	1.05
Liver	1.27	1.17	1.03
Blood	0.96	0.71	0.73

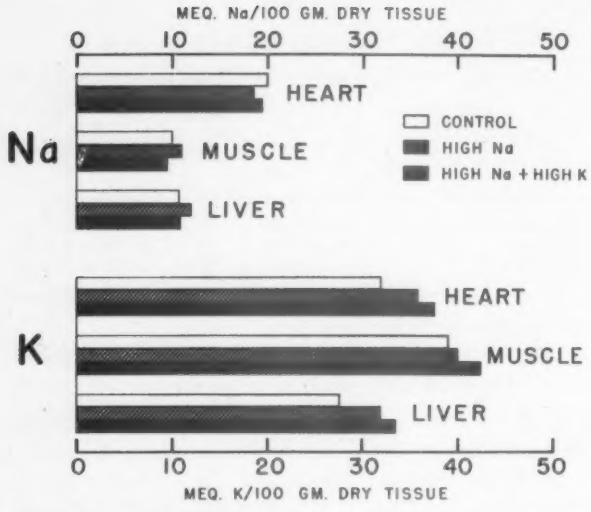

FIG. 2. Average concentrations of Na and K in dry tissue.

muscle and liver agreed well with those of serum from the three groups of animals. This indicates that complete mixing of radioactive potassium with body potassium had occurred and also suggests that in these experiments serum was a representative body sample for the estimation of $(K)_E$ by the method of isotope dilution.

4. Tissue Sodium and Potassium Concentrations: Na and K concentrations were measured in heart, muscle, liver, bone, blood and plasma taken from the animals used for estimation of $(K)_E$, including (A) eight control rats, (B) eight rats fed 4 per cent Na and (C) eight rats fed 4 per cent Na + K. In Figure 2 and Table VI are shown the average concentrations of Na and K expressed as milliequivalents per 100 grams dry tissue. The individual values varied considerably so that in most cases the differences shown between group averages were not statistically significant. A trend is to be noted in the electrolyte pattern of tissue from the three groups of animals. The Na content of hearts from rats fed 4 per cent Na was lower than hearts from control rats or those fed 4 per cent Na + K. Rats fed the high Na + K diet had normal concentrations of Na in the heart. Muscle Na was higher in the group fed large amounts of Na than in the control or those fed both high Na + high K and the Na concentration in the muscle of the latter was similar to that of control animals. The Na content of liver followed the same pattern as muscle. Measurement of K in heart, muscle and liver from the three groups revealed that control rats had the lowest concentrations of K; rats fed high levels of Na had more K in their tissues than control rats,

TABLE VI
Effect of Added Dietary KCl on Tissue H_2O, Na and K

Organ	Diet		
	Control	4% Na	4% Na + K
	A. H_2O (Per cent fresh tissue weight)		
Muscle	73.4 ± 0.18*	74.3 ± 0.44	75.0 ± 0.25
Heart	78.0 ± 0.22	78.0 ± 0.18	78.4 ± 0.28
Liver	70.5 ± 0.60	71.8 ± 0.24	71.9 ± 0.26
	B. Na(mEq./100 gm. dry tissue)		
Muscle	10.0 ± 0.34	11.0 ± 0.73	9.3 ± 0.34†
Heart	20.0 ± 0.63	18.7 ± 0.83	19.6 ± 0.94
Liver	10.9 ± 0.91	12.0 ± 1.03	11.0 ± 0.70
	C. K(mEq./100 gm. dry tissue)		
Muscle	39.0 ± 0.64	39.9 ± 0.91	42.4 ± 0.67†,‡
Heart	31.9 ± 0.78	35.7 ± 1.09‡	37.7 ± 0.89‡
Liver	27.5 ± 0.53	31.9 ± 0.96‡	33.4 ± 0.46‡

* Standard error of the mean.
† Significantly different from 4 per cent Na ($p < 0.05$).
‡ Significantly different from control ($p < 0.05$).

while the group fed diets high in both Na and K had the largest amount of tissue K. In general the Na and K concentrations of tissue samples reflected the values for exchangeable body Na and K in the three experimental groups. The one exception was the relatively low Na concentration in hearts of rats fed large amounts of Na. Subsequent measurements on hearts of other animals subjected to this same dietary treatment for different lengths of time have not confirmed this finding. Hence, its meaning is not clear.

Na and K concentrations were also measured in bone, blood and plasma from these same three groups of animals (Table VII). Bone was studied because it seemed possible that after long-term experiments of this kind some of the excessive dietary Na or K might have been deposited there and not be measured as $(Na)_E$ or $(K)_E$. The Na and K concentrations in bone from the three groups were equivalent in spite of the wide differences in electrolyte compositions of the diet. The Na and K concentrations of both whole blood and plasma were also quite similar in the three groups, indicating no appreciable changes in the electrolyte concentrations of the red blood cells.

COMMENTS

In these experiments chronic NaCl toxicity was associated with increased exchangeable and total tissue Na although it is not possible to

TABLE VII
Na and K Content of Bone, Blood and Plasma

Substance	Na Content			K Content		
	Control	4% Na	4% Na + K	Control	4% Na	4% Na + K
Bone (mEq./100 gm. fat-free solids)	31.4 ± 0.63*	31.5 ± 0.61	31.4 ± 0.53	4.21 ± 0.12	4.19 ± 0.18	4.04 ± 0.08
Blood (mEq./L.)	85 ± 4.4	85 ± 3.9	85 ± 1.4	55 ± 4.0	55 ± 3.3	56 ± 1.5
Plasma (mEq./L.)	154 ± 1.4	144 ± 4.7	148 ± 1.2	5.35 ± 0.39	4.88 ± 0.27	5.16 ± 0.36

* Standard error of the mean.

state whether this was the cause, effect or an accompanying phenomenon of the hypertension and shortened life span seen in Na intoxicated animals. It is of interest that increased body Na occurred without an accompanying reduction (below control levels) of exchangeable or total tissue K. The Na:K ratio of the tissues studied were equivalent in control animals and those fed large amounts of NaCl, which suggests that the observed increase in body Na was not the result of replacement of intracellular K by Na. The serum Na levels were quite similar in all groups which indicates equivalent concentrations of Na in the extracellular fluid. Although no estimations of extracellular or intracellular compartments were attempted in these animals, the Na space was markedly increased in those animals having elevated body Na. If one accepts the premise that Na space approximates extracellular space, the observed increase in tissue Na might have resulted from an increased extracellular compartment in these animals.

The addition of K to diets containing large amounts of NaCl appeared to furnish partial protection against the hypertension and shortened life span seen in rats fed toxic levels of NaCl. Rats fed supplementary K also maintained normal $(Na)_E$ and tissue Na concentrations in spite of excessive dietary NaCl. Retention of Na was not related to the absolute amounts of Na in the diet but rather to the dietary Na:K ratio.

SUMMARY

Sodium space, $(Na)_E$, $(K)_E$ and tissue concentrations of Na and K were measured in rats fed various levels of Na and K.

Those fed diets high in NaCl with added K lived longer and had less hypertension than those on the same high levels of Na without added K.

Rats fed diets containing more than 2 per cent Na had increased Na space, $(Na)_E$ and tissue Na. Sodium space, $(Na)_E$ and tissue Na concentrations were not elevated in animals fed the same high levels of NaCl plus KCl added to maintain a less distorted Na:K ratio.

$(K)_E$ and tissue K concentrations were similar in controls and rats fed high Na. Those fed large amounts of both Na and K had higher $(K)_E$ and tissue K.

The Na and K content of serum, blood and bone was not changed by the dietary levels of these elements.

REFERENCES

1. MENEELY, G. R., TUCKER, R. G. and DARBY, W. J. Chronic sodium chloride toxicity in the albino rat. I. Growth on a purified diet containing various levels of sodium chloride. *J. Nutrition*, 48: 489, 1952.
2. MENEELY, G. R., TUCKER, R. G., DARBY, W. J. and AUERBACH, S. H. Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and of a syndrome of edema and renal failure. *J. Exper. Med.*, 98: 71, 1953.
3. TUCKER, R. G., BALL, C. O. T., DARBY, W. J., EARLY, W. R., KORY, R. C., YOUMANS, J. B. and MENEELY, G. R. Chronic sodium chloride toxicity in the albino rat. III. Maturity characteristics, survivorship, and organ weights. *J. Gerontol.*, 12: 182, 1957.
4. MENEELY, G. R., BALL, C. O. T. and YOUMANS, J. B. Chronic sodium chloride toxicity. The protective effect of added potassium chloride. *Ann. Int. Med.*, 47: 263, 1957.
5. MENEELY, G. R., DARBY, W. J., LEMLEY-STONE, J., TUCKER, R. G., BALL, C. O. T. and YOUMANS, J. B. Chronic sodium chloride toxicity. The protective effect of added potassium chloride. *Circulation*, 14: 501, 1956.
6. KERSTEN, H., BROSENE, W. J., JR., ABLONDI, F. and SUBBA ROW, Y. A new method for the indirect measurement of blood pressure in the rat. *J. Lab. & Clin. Med.*, 32: 1090, 1947.
7. LOWRY, O. H. and HASTINGS, A. B. Histochemical changes associated with aging. I. Methods and calculations. *J. Biol. Chem.*, 143: 257, 1942.

Panel Discussion

Chairman: Dr. Frank M. Sturtevant

DISCUSSION OF PAPERS BY HALL AND HALL; DAHL; FREGLY; FREED; STAINSBY AND RENKIN; AND LEMLEY-STONE, DARBY AND MENEELY

DAVID GORDON (Miami, Fla.): I would just like to confirm some of this work and point out to Dr. Meneely that he should not have been too surprised by the fact that his salt-hypertensive rats lived longer when given potassium but still had higher blood pressures. Dr. Freed demonstrated the same thing (*Proc. Soc. Exper. Biol. & Med.*, 78: 77, 1951). He administered DCA to rats, fed them salt in the usual manner, and they became hypertensive. Their survival rate, however, was not good. As a control for some other experiments with low potassium levels, he administered DCA and KCl to one group. These rats had higher blood pressures than the salt-fed rats but they lived longer and, in general, they seemed to do better. Dr. Drury and I noted the same thing with renal hypertensive rabbits (*Circulation Res.*, 4: 167, 1956). Some rabbits were given KCl to drink and some were untreated as control subjects. All were maintained on the regimen until they died. The KCl-treated rabbits lived longer but their blood pressures were higher than the control rabbits. This does not explain your finding, but it certainly confirms the same phenomenon.

GEORGE MENEELY: We claim no credit for the idea that potassium might be of some help in hypertension. I think Priddle is the one who first proposed potassium for the treatment of hypertension (*Canad. Med. A. J.*, 25: 5, 1931).

SIMON KOLETSKY (Cleveland, Ohio): I want to comment on Dr. Fregly's paper concerning potassium and that will lead me into a comment on Dr. Meneely's work. From time to time we have made some observations on the effect of drinking KCl instead of NaCl as well as having the rats drink both at one time. None of these observations is published. NaCl is a nephrosclerotic agent; it is very injurious to the kidney, especially to the glomeruli. This is not true of potassium. If you feed potassium on a fairly long-term basis to rats and accelerate development of hypertension by reducing renal mass, a very interesting difference begins to appear. Obvious or significant glomerular disease does not develop in the potassium-treated rat but a tubular type of lesion which is characterized by marked swelling and proliferation of the tubular lining cells does develop. It is a type of lesion different from that produced by sodium. When Dr. Fregly talked about his experiment with potassium, he said that the kidneys both from sodium- and potassium-treated rats were enlarged. However, they are different morphologically, although I agree that in our experience potassium alone also has had a tendency to produce elevation in pressure. You mentioned that the adrenal was enlarged with administration of potassium. We have also noted this, but cannot corroborate the reverse observation because in our experience with sodium-fed animals, the adrenal is not comparably enlarged. In fact, it was our guess that the blood pressure is elevated in the potassium-fed rats through an adrenal-cortical mechanism which promotes retention of sodium.

About Dr. Meneely's work: I think that there is no question but that he has shown a definite protective effect as a result of potassium. I wonder whether the protective effect of the potassium is not exercised directly in the tissues. In other words, by giving the combination and exposing the tissues to added potassium one might be reducing the toxicity of the sodium. Finally, I still am not sure why Dr. Meneely postulates two different kinds of hypertension. Perhaps there are two different manifestations of the same kind of hypertension. In one instance, by means of a protective element in critical places, you do not get the same kind of vascular disease and the same degree of elevation of blood pressure, but the two are not fundamentally different. Postulating two different kinds of hypertension makes it appear that there are two radically opposed mechanisms, which I think is questionable.

JAMES CONWAY (Ann Arbor, Mich.): I would like to ask a basic question as an extension of Dr. Koletsky's comments. Can salt produce hypertension without first damaging the kidney? Has anybody information on the reversibility of this type of hypertension? If you administer salt for a period of time, can you stop the salt and have a return of blood pressure to normal units? This might indicate whether there is renal damage.

CHARLES HALL: Dr. Friedman first reported that for DCA-hypertension (*Canad. Med. A. J.*, 61: 596, 1949). We have had the same experience. When rats get hypertension on salt and you take the salt away, the hypertension remains. Dr. Dahl told me of a similar experience in his laboratory. When animals become hypertensive from salt-eating, they do not lose the hypertension when salt is discontinued.

JAMES CONWAY: Is there a period of time when the salt has a direct vascular effect, say in the first week or two, when it would be reversible? When do renal changes appear?

CHARLES HALL: If there are renal changes, they are not detectable by conventional methods.

MELVIN FREGLY: I could set an outside limit to your question, Dr. Conway. After 10 weeks of administration of 1.9 per cent NaCl solution as the sole drinking fluid, the hypertension is not reversible. Take away the NaCl solution and the rats remain hypertensive. But that is an outside limit, and I cannot tell you what would happen in a week or 2 weeks.

SYDNEY FRIEDMAN (Vancouver, Canada): These comments are in connection with the question which Dr. Conway raises and also in connection with what Dr. Dahl said earlier. I cannot answer the questions about renal function and its changes with salt feeding alone, but I would like to point out our study. Some 10 years or so ago we carried out a study of the effects of various sodium salts on DCA hypertension and its reversibility (*Am. J. Physiol.*, 153: 226, 1948). We found that of all the anions, phosphate had a particularly toxic effect; perhaps that observation has some bearing on Dr. Dahl's sea salt. I would like also to make the point that although renal clearances appeared to be unchanged in the early phases of DCA-salt treatment, in actual fact the kidney was enlarged quite early and there was a compensatory hypertrophy which meant that the actual function of a gram of tissue was reduced (*J. Exper. Med.*, 89: 631, 1949). It is quite difficult to do Tm studies in the rat which is the animal of choice in this case. This fact makes it rather difficult to establish how early the functional changes occur. With salt hypertension I imagine the same would be true. With DCA hypertension we also studied periods of reversibility ranging from about 2 weeks to about 6 weeks. It would reverse even at 6 weeks but beyond that the time became critical and I would guess that salt hypertension would be roughly similar.

RENÉ GIRERD (Morris Plains, N. J.): I would like to ask Dr. Hall if he has an explanation for the apparent discrepancy between the mortality rate of the animals he treated with DCA and lithium chloride and the incidence of lesions which were observed in these animals. If I recall it correctly, he found an incidence of 100 per cent for lesions of heart and kidney with lower mortality as compared with animals treated with DCA and sodium.

Regarding the problem of corticoid hypertension in hypophysectomized rats we have been working along similar lines although we have used different approaches. In the first place, we used male rats and found them to be preferable to females because most people working in the field had been using male rats and because it is much easier to verify the completeness of hypophysectomy which sometimes can escape visual observation. Incompletely hypophysectomized rats have a marked increase in testis size. In our experience, when we had properly hypophysectomized male rats, the size of the testis was not even one-tenth the size that we observed in nonhypophysectomized animals. I think the use of female rats has been reported previously by Selye's group (*Ann. Endocrinol.*, 14: 366, 1953) and I am wondering if sex could cause a difference between Dr. Hall's results and ours; we noted that the administration of desoxycorticosterone acetate in sensitized hypophysectomized male rats was unable to raise the blood pressure or to cause any hypertension. The only additional treatment which would eventually produce a change and raise blood pressure would be the administration of various pituitary preparations, one of them being lyophylized anterior pituitary or a composite of somatotrophic hormone, ACTH and pitressin.

CHARLES HALL: We have no direct experience with male rats, and it was drawn to our attention in one of our publications by the editor that all the people who had reported failure of hypophysectomized animals to respond to DCA had, in fact, used male animals. I myself cannot conceive of any fundamental difference in hypertensive disease between a female and a male, and I doubt that this can be the explanation. On the other hand, I have no direct evidence of this. Secondly, I have no explanation for the increased mortality of animals on NaCl whose hypertension is no greater than those on lithium chloride. There must be some other aspect of sodium toxicity which is not reflected in blood pressure and which leads to mortality, since we customarily find this greater mortality among the DCA and salt-treated animals than among DCA and lithium-treated animals even though the elevation of blood pressure is the same.

SIMON KOLETSKY: Could you say there was a greater incidence of infection? Many of these rats get pneumonia and die. This is particularly true of sodium-loaded animals.

CHARLES HALL: We have found pneumonia. I am not quite sure this was the cause or the effect, but it does occur.

With respect to the other questions regarding the criteria used as for completeness of hypophysectomy, we have used several more or less concurrently: In the first place, the failure to grow, which may or not be an adequate measure; secondly, the failure to develop the typical guard hairs or rough fur, which the intact animal shows and which in the hands of Rennels and Everett (*Anat. Rec.*, 135: 21, 1959) has been the most sensitive criterion of completeness of hypophysectomy. If a small quantity of tissue is present which does not cause the animal to grow, it will still cause the development of the typical guard hairs which is associated with tracer amounts of LH. We have used this also. It has been reported that DCA exerts a tropic effect on the testis of the hypophysectomized animal (*Arch. path. Anat.*, 321: 559, 1952), and we believed that, if this were true, it would be very difficult to test the completeness of hypophysectomy in a DCA-treated animal. Therefore, we have not attempted to study this in the male. I have no explanation other than the possible role of sucrose or the possible effect of a more fully de-

veloping hypertension as a consequence of a lower dose of DCA. These are things which are in my mind; I have no proof for any of them.

FLOYD SKELTON (New Orleans, La.): I wanted to ask Dr. Fregly if he has looked at the adrenals of any of his animals which received potassium nitrate, particularly with reference to the width of the zona glomerulosa? Since this substance probably alters the sodium-potassium ratio in favor of potassium, one might expect increased width. If there were increased width and increased functional response, this might complement some observations of Gornall (*Canad. J. Biochem. Physiol.*, 35: 113, 1957) who has shown that small amounts of alderosterone administered to animals in the absence of excessive salt intake are capable of producing hypertension.

MELVIN FREGLY: The tissues from all the rats that we have used are now with Dr. Hood in the pathology laboratory. Before the conference began, I asked him if he could tell me off hand what he had observed. Dr. Hood told me that of the tissues he had looked at, the most striking changes occur in the adrenal. With routine staining, he sees increased width of the glomerulosa and with fat stains and lipid droplets can be seen in the glomerulosa. He has only done routine staining on the other tissues at the present time.

SIMON KOLETSKY: We can confirm that the glomerulosa is definitely increased. We didn't do fat stains.

OCTAVIA HALL: I would like to comment a little further on Dr. Conway's question on the reversibility of hypertension. In clipped hypertension it was our experience that if you took out the offending kidney at a mild level of hypertension and reversed the hypertension, there was no morphologic change. The other comment I would like to make is about a detail from Dr. Fregly's experiment, in which the level of blood pressure in the control animals seemed high until I noticed the body weight. These are large and older animals. In our experience, older rats do have control values that are higher.

FRANK STURTEVANT (Evansville, Ind.): I certainly can agree that blood pressure is usually directly proportional to body weight. However, I cannot agree that an indirect blood pressure of 140 mm. Hg is necessarily a high value. The absolute value of an indirect blood pressure reading is, to me, meaningless and, therefore, cannot be compared to readings from other laboratories. Only changes in indirect pressures observed by the same person in the same laboratory would appear to be of significance.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

The Innocent Systolic Murmur in Children

THE INNOCENT systolic murmur is the most prevalent cardiac sign in children. Phonocardiographic studies reveal this murmur in all children, although it is not always audible with the stethoscope. Dr. D. H. Fogel (*Am. Heart J.*, 59: 844, 1960) has recently described three types of innocent systolic murmur:

1. *Parasternal-Precordial:* This is the most common type of murmur. It occurs usually between 3 and 12 years of age, and is most frequent among 6 year old children. It is vibratory in nature. The greatest intensity is in the third or fourth intercostal space to the left of the sternum, or between the sternum and the apex. Intensity varies between grades 1 and 3. The pitch is medium and duration is brief, occupying the first half or two-thirds of the systole. It can be transmitted to the axilla, or, in thin children, to the infrascapular area. Intensity varies with position and with the follow-up examination.

2. *Pulmonic:* This is the second most common murmur, and occurs over the base or pulmonic area during the first part of systole. It is short and blowing, varies in intensity from grades 1 to 3, and is transmitted parasternally toward the apex. The second pulmonic sound is normal. The intensity of the murmur varies with position and with follow-up examination. This murmur is the most common innocent murmur among adolescents. In children and flat-chested persons, little lung tissue intervenes between the pulmonary conus and the sternum, and consequent slight distortion of the vessels may cause the pulmonic murmur. Compression of the pulmonary artery by the chest wall may produce the murmur in patients with pectus excavatum, kyphoscoliosis or abnormal cardiac position.

3. *Cardiorespiratory:* This murmur is infrequent in children. It is heard at the apex or over the body of the heart at the lung margins as a high-pitched, short squeal. It is nearly always systolic in time and sharply located.

In a clinical study of 231 children between the ages of 1 month and 17 years referred to a cardiac clinic, 66.7 per cent had innocent murmurs. Of 124 parasternal-precordial murmurs, 111 were in children less than 10 years old. Twenty pulmonic murmurs were heard. Twelve of these children were past 11 years. Only two cardiorespiratory murmurs were heard. Eight of eleven patients with rheumatic fever had innocent murmurs.

Myxoma of the Left Atrium

ALTHOUGH myxomas of the left atrium are rare, their ability to masquerade as mitral valvular disease warrants their constant consideration. This is particularly true in those patients who present any atypical features in the clinical picture.

Awareness of this tumor is the best clinical tool. Armed with this the clinician can better appreciate the subtleties in which this condition is likely to reveal itself. Careful attention to the course and duration of symptoms, their variability with body position and improvement following embolic phenomenon is essential. Differences in the described findings on auscultation by separate examiners or by the same examiner is a significant lead. This variability may be confirmed on phonocardiographic study. Cycle to cycle variation in the second to third sound interval is noteworthy.

Electrocardiographic study is essentially of no help in making a distinction. Roentgenographic examination by revealing pulmonary artery and right ventricular enlargement in the face of a small left atrium is significant. The routine right heart catheterization is usually of little assistance. Left atrial puncture may be catastrophic.

In spite of the several diagnostic hints, angiocardiography remains the only definite means by which a preoperative diagnosis can be made. With the new technics of open heart surgery, these tumors can now be safely removed and

complete cure effected. To date, at least twenty successful operations have been recorded. The diagnosis was made preoperatively by angiocardiography in only five of these cases. The diagnosis in the other cases was made during surgical operation for mitral valvular repair.

Drs. T. E. Hair, Jr., E. S. Orgain, W. C. Sealy and H. D. McIntosh (Duke University Medical Center, Durham, North Carolina) have recently operated on two patients, both adults, who had atypical signs for mitral stenosis. In one, the development of acute pulmonary venous engorgement, strikingly more pronounced in one lung field, was noted. The pedunculated character and bizarre shape of the successfully removed tumor make selective pulmonary vein obstruction a likely explanation of the described phenomenon. This is a finding which, in future cases, may prove of aid in initiating further diagnostic studies. Cineangiography in the second case excellently demonstrated the quite large and mobile tumor which was also successfully removed.

Letter to the Editor

Endocardial Fibroelastosis

Dear Editor:

With reference to an article by Paul, R. N. and Robbins, S. G., "Surgical Treatment for Endocardial Fibroelastosis or Anomalous Left Coronary Artery" (*Am. J. Cardiol.*, 1: 694, 1958).

I have a family under my care in which two children have already died in infancy with subendocardial fibroelastosis. The third baby is now aged 5 months and so far symptoms have not developed. However, the previous two babies were well until the age of about 6 months.

Would you please comment on the present value of pericardial poudrage so that I could inform the parents of prospects of surgical treatment, if this baby should have fibroelastosis.

V. B. Henry, M.D., F.R.C.S. (Edin.)
Townsville, Australia

REPLY BY DR. PAUL

Dear Editor:

There is no appreciable change in the status of these patients since the last report in The American Journal of Cardiology in 1958. This article dealt with a 4 year experience, and this can now be altered to approximately $7^1/_2$ years. All of the patients that survived surgery, with the exception of the one already quoted as having died 5 months postoperatively, are living and well, none having taken any further digitalis or encountering any further difficulties. There have been approximately twelve more patients operated on in the same manner since the original ten cases were reported, and all have done quite well. We have, unfortunately, not been able to follow personally all the patients in this group, but through communication with parents or doctors in various portions of the country where these patients are, the indications are that they too are doing quite well. We have had no reports on subsequent deaths in any of these patients, and thus far still hold that this procedure apparently sustains life well beyond the expected longevity in this group, which, according to most statistics, will average 90 to 95 per cent mortality in the first 2 years of life. We do not contend that it is curative, since there seems to be no logical reason why the fibroelastic lining should disappear, but by way of our experience we would have to recommend that this procedure be offered to patients with endocardial fibroelastosis or anomalous left coronary until such time as a better procedure may be offered.

Raphael N. Paul, M.D.
Memphis, Tennessee

Book Reviews

Current Therapy—1961, edited by Howard F. Conn. W. B. Saunders Co., Philadelphia, 1961, pp. 806, $12.50.

This latest edition of Current Therapy contains a fifty-five page section on the cardiovascular system. Of special interest are the concise summaries of the treatment of Adams-Stokes attacks, paroxysmal tachycardia and atrial fibrillation, bacterial endocarditis, hypertension and myocardial infarction. S. D.

Pharmacology—The Nature, Action and Use of Drugs, 2nd ed., by Harry Beckman, M.D. W. B. Saunders Company, Philadelphia and London, 1961, pp. 805, $15.50.

The rapid development of pharmacology as a science and the phenomenal increase in the number of drugs in current use is attested to by the appearance of the second edition of this popular textbook only three years after its introduction to the market. The title has been changed from Drugs—Their Nature, Action and Use, to the more definitive title stated above. The book has also grown in size, with seventy-seven more pages and an increase in the number of chapters from seventy-six to eighty-one. Some compression has been noted, with the elimination of some illustrations and reduction in the size of type used for the references at the end of each chapter. However, Dr. Beckman has succeeded admirably in condensing the vast amount of new material available to a workable minimum and deleting much obsolete material.

The new edition retains the attractive first person style in writing which characterized the first edition, and Dr. Beckman's frank appraisal of many drugs will emphasize that there are divergent opinions among physicians regarding the usefulness of drugs available for many purposes. Some chapter titles have been reworded—which causes one to wonder if this represents the development of skepticism regarding the efficacy of certain drugs or whether the author is merely trying to be more precise in categorizing drug action. For example, Chapter 27 is reworded "Drugs that are Used Principally for Vasodilation in Coronary Disease," from "Drugs that Dilate the Coronary Arteries"; and Chapter 28, "Drugs that are Used Principally for Vasodilation in Hypertension," from "Drugs that Reduce Blood Pressure." Readers of this Journal will appreciate two new chapters entitled "Drugs that are Used Principally for Vasodilation in Peripheral Vascular Diseases" and "Drugs that are Beneficial in Hepatic Coma." The chapter on Hypertension, in this reviewer's opinion, is a great improvement over the corresponding chapter in the first edition. The chapters on "The Pharmacology of the Autonomic Nervous System" have been rearranged, with first consideration being given to parasympathetic agents. The material on "The Pharmacology of Drugs in a Miscellany of Specific Categories" (thirteen chapters!) has been rearranged and revised, as has the material on Chemotherapy, now under the heading "Pharmacology of Infection and Infestation." The index has been greatly expanded from forty-three triple-column pages to fifty-six pages in smaller type. Altogether, one gets the impression that the book has greatly improved over the previous edition.

The references to original articles at the end of each chapter are a most useful and attractive feature of this book. The several thousand references collected in this volume will save hours of searching for original papers and will be of inestimable value to those seeking additional information on some drug or pharmacologic method. More liberal use of structural formulas (all neatly drawn and nicely proportioned) attests to the growing importance of organic chemistry to pharmacology. Like the first edition, this treatise is neatly printed on durable paper and attractively bound. It is a beautiful book revealing precision of method, completeness of subject matter, and broad experience on the part of the author. It can be most profitably studied by students, research workers, clinicians and all who are anxious to learn more about the fascinating science of pharmacology. JOHN C. KRANTZ, JR.

Myocardosis. Pathogenesis, Clinical Aspects and Therapy Concerning the Principles of Metabolic Electrocardiography, by Ferdinand Wuhrmann and Serge Niggli. Charles C Thomas, Springfield, Illinois, pp. 218, 1960, $10.50.

The term myocardosis is summarized by Wuhrmann and Niggli as "a functional, protein metabolic impairment of the heart muscle in which dysproteinemia and paraproteinemia are often but not always seen and in which the underlying disease processes are variable." (They call this pure dysproteinemic myocardosis.) "It is purely functional and reversible at the outset. Prolonged duration and repeated exacerbations of the late stage in which nonspecific myocardial changes, particularly fibrosis, are seen, but which are often no longer primarily metabolic in nature, can ultimately result in the frequently seen clinical picture of hemodynamic myocardial insufficiency." In addition, a type of combined myocardosis can occur due to electrolyte distrubances and the simultaneous occurrence of vitamin (particular B_1 and B_2) or hormone (e.g., adrenal, thyroid) imbalance.

The terms dysproteinemia and paraproteinemia refer to derangement of the serum albumin and globulin. These disturbances are detected by means of paper electrophoresis or by the sedimentation rate test in conjunction with the Weltmann Reaction and other procedures.

Wuhrmann and Niggli continue: "The electrolyte balance of the organism, and particularly the distribution of the electrolytes in the blood, primarily potassium, sodium and calcium, are closely and reciprocally related to the blood proteins and their pathologic alterations. The healthy organism is characterized by a simultaneous euproteinemia and euelectrolytemia. The primordial clinical significance of the blood proteins which maintain isoionia, isotonia and isohydria, is demonstrated by the fact that under pathologic conditions, dysproteinemias and dyselectrolytemias are most frequently seen, while euproteinemias with simultaneous dyselectrolytemias are rarely encountered . . . ."

"The clinical manifestations of myocardosis are often discrete. In the foreground are generalized tiredness, reduction of ability to work, noticeable changes of pulse frequency (especially a propensity for moderate tachycardia), more rarely dyspnea and cyanosis, and refractory behavior with respect to cardiac active glycosides. During the early stages the heart is not enlarged and no signs of congestion are present and a tendency toward hypotension is observed. Gallop rhythm is rarely seen. More frequently an impure or diminished first heart sound, heard best over the apex, is encountered. During the late stages after a duration of many years, myocardosis cannot be differentiated from other forms of hemodynamic myocardial insufficiency."

Electrocardiographic changes include: depression or disappearance or inversion of the T waves, fusion of S-T and T, low voltage of QRS, prolongation of the Q-T interval, and return to normal following normalization of the metabolic disturbances.

"The most important disease groups in which myocardosis may be encountered are: subacute and chronic diseases and intoxications and their aftermaths as they apply to the liver, the kidneys and the pancreas; chronic gastric and intestinal diseases including hunger and deficient nutrition; infectious diseases; malignant tumors and hemoblastoses; comatose states of varying etiologies; hormonal disturbances, pregnancy, major surgical procedures, etc."

In studying electrocardiographic patterns, the authors paid particular attention to the frontal plane leads and made extensive mathematical calculations of instantaneous time vectors, ventricular gradient and other measurements.

The book is divided into ten chapters. There are chapters on the symptomatology and special forms of the myocardosis syndrome, as well as conventional descriptions of the electrocardiographic patterns of hypopotassemia, hyperpotassemia, hypocalcemia, and hypercalcemia. The use of cumbersome terminology and the lack of any clearcut differentiation of electrocardiographic changes due to electrolyte disturbances from those due to the myocardosis syndrome make for difficult reading.

EMANUEL GOLDBERGER, M.D.

The Treatment of Hypertension, by Sir George Pickering, William Ian Cranston and Michael Andrew Pears. Charles C Thomas, Springfield, Illinois, 1961, pp. 175, $7.00.

This monograph is 175 pages long including index and references. It is an excellent attempt to correlate the biochemistry, physiology and clinical manifestations of hypertension, with a rational approach to therapy as reflected in control of the blood pressure. Whether the reader agrees or disagrees with the proposed concepts makes little difference in final analysis, since the conclusion is that blood pressure control improves prognosis as reflected in both morbidity and mortality.

The book is quite up to date for a field which is

changing so rapidly. It is quite apparent that the chemical properties of the drugs used to treat hypertension are much better understood than is the chemistry of the disease itself. In the foreword, Dr. Kugelmass states that one purpose of the monograph series is to "explain clinical phenomena in chemical terms," and this has been achieved in part by the authors. Unfortunately, this is not so easy to do in a disease in which the cause and underlying mechanisms are not known and the effect of treatment of the body chemistry is not understood—which leaves the therapist with the empirical conclusion that treatment is good, but why, or how, nobody knows. Consequently, an adequate understanding of the drugs used in the treatment of this syndrome becomes increasingly important not only in relation to therapy but even more in relation to etiologic mechanisms, since it seems apparent that the clinical pharmacologists have learned more about hypertension in the past decade than the clinical physiologists and geneticists have been able to determine in the past century.

College News

PRESIDENT'S COLUMN

The Thin Thread of Organization

On a previous President's Page, a description was made of the amazingly small employed staff which is maintained by this College, 2.5 persons to be exact. With a total membership of 2,000, with more than 2,000 physicians attending our programs, with hundreds of applications to be reviewed yearly, with several hundred abstracts to be reviewed for the annual meeting, with honorary Fellows and Lecturers to be selected, with convention arrangements, exhibit arrangements, banquet arrangements, convocation arrangements, Work Shop arrangements and now the Young Investigators to be judged, it is apparent that some very real form of organization must exist. This formal organization is, of course, the Officership of the College and the committees of the College. The officers are elected by the College, the Committees appointed by the officers. The policy-making group is the Board of Trustees. One of my greatest enthusiasms for our College is the fact that a Trustee can serve but 5 years and that the President under no circumstances may hold any office after his term as a Trustee. In other words, there is no permanent hierarchy, the thin thread of organization is given strength not by any single group of invested power; the thread gains its strength entirely from the shared ideals and enthusiasm of the Officers. No elected Officer is compensated. The Nominating Committee, responsible for proposing the slate of Officers, is, by tradition, not contacted by the Trustees and, by tradition, three of its five members must come from the general membership of the College and not from the Board of Trustees. This is indeed an organization by, from and for physicians. The thin thread of organization suits it well and long may the organization prosper if it continues its flexible, sensitive means of administration, bringing young men on the Board of Trustees, sustaining its strength by the imagination, vigor and ideals of the membership of the College.

E. GREY DIMOND, M.D.
President

American College of Cardiology

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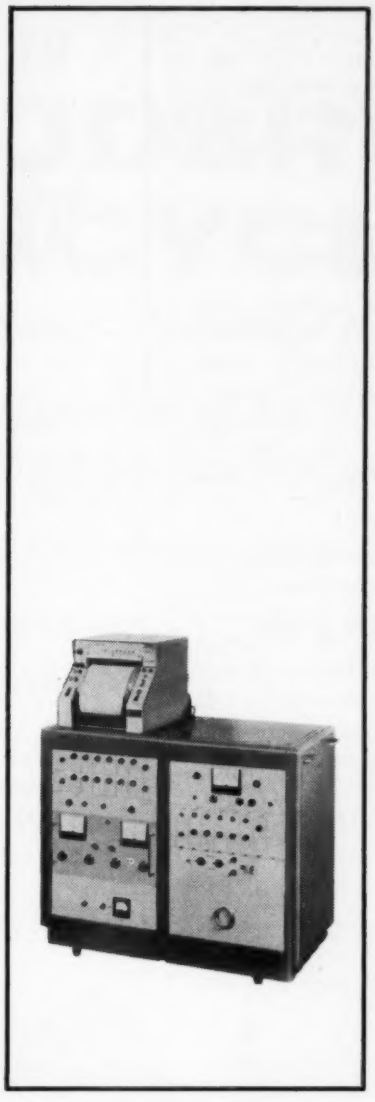

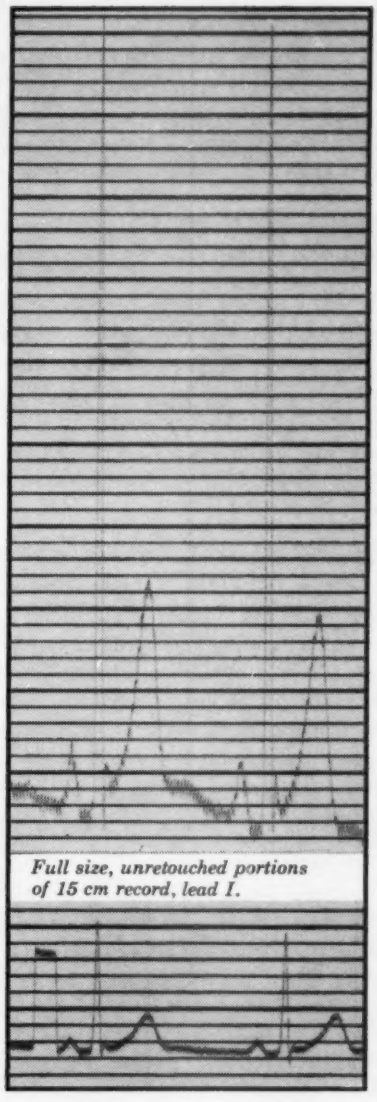

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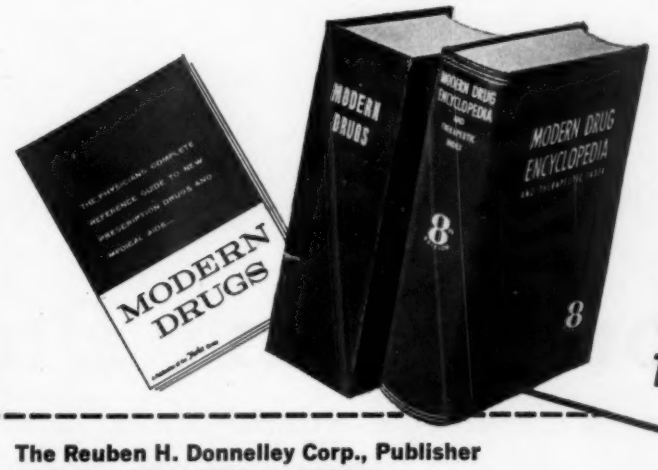

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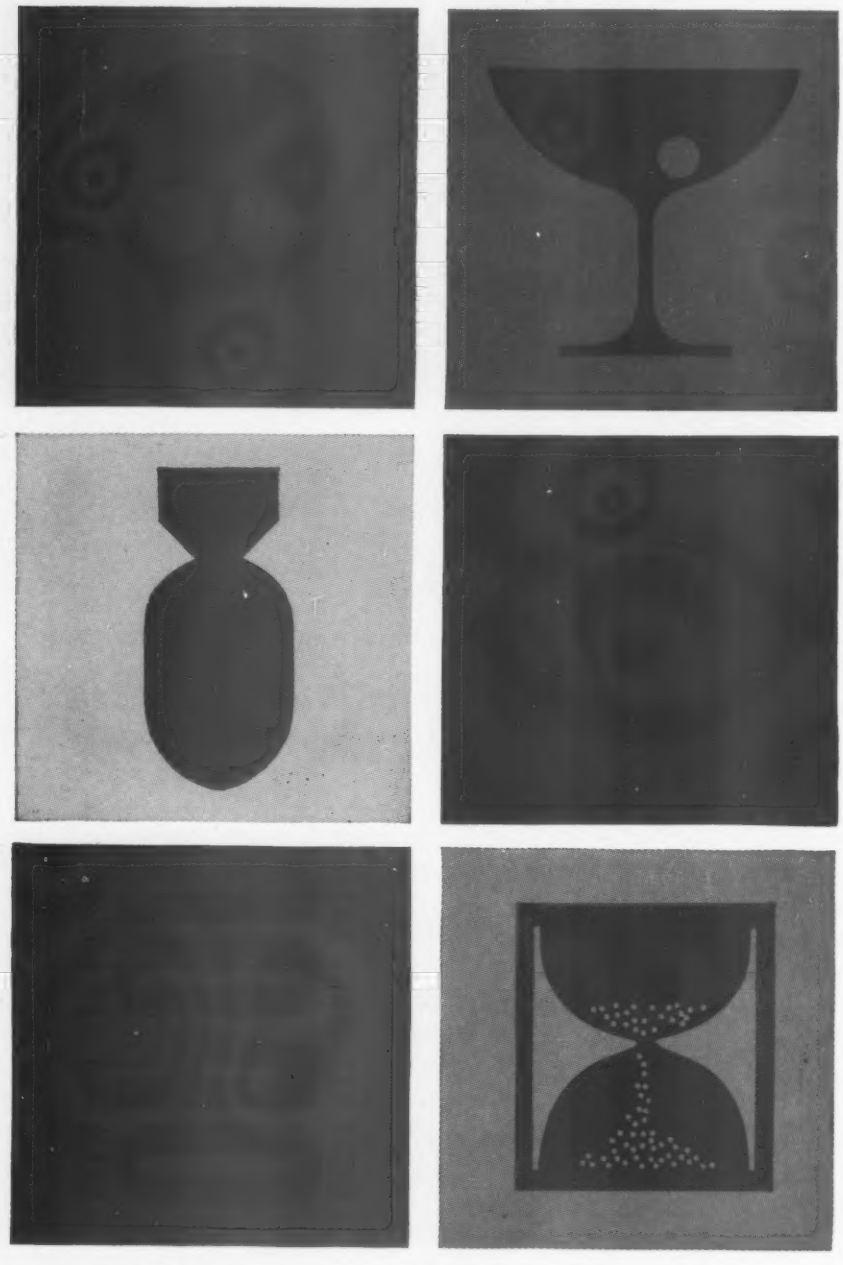

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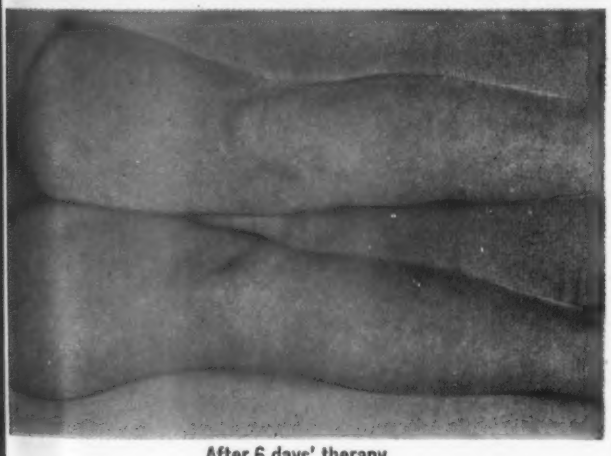

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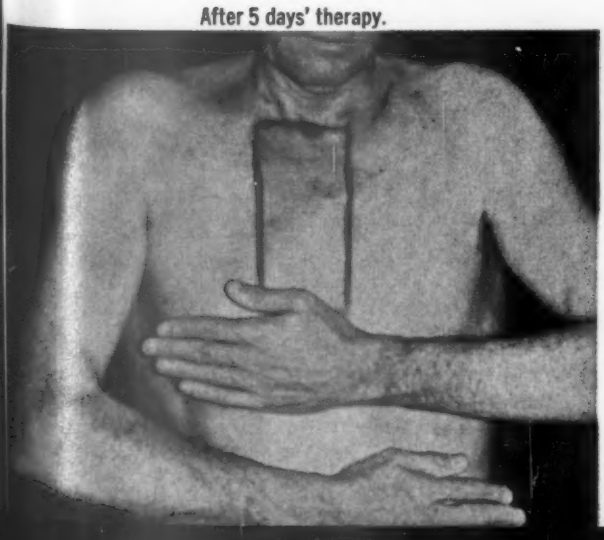

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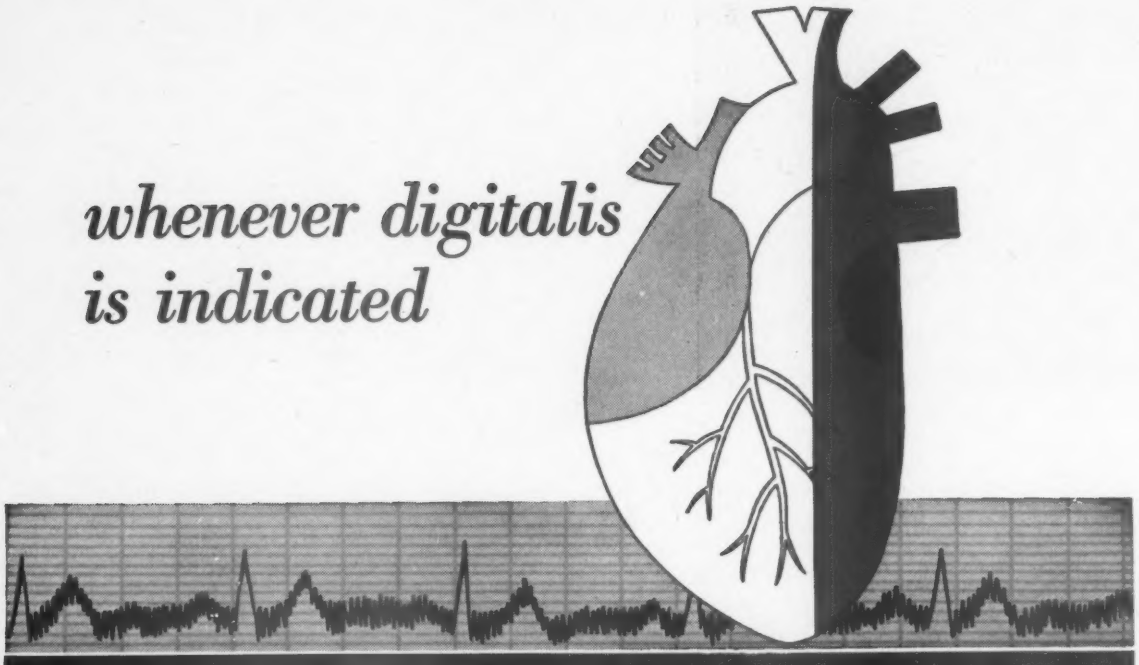

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formerly known as Digoxin 'B. W. & Co.'

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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0.25 mg. scored (white)
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0.5 mg. in 2 cc. (I.M. or I.V.)

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0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

DRAMATIC
physical and emotional relief in
ANGINA PECTORIS

'round-the-clock protection against both pain and fear

COROVAS

Tymcaps

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

SUPPLIED—Boxes of 60 and 120.

PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.
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INJECTION

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(metaraminol)

"...A strong pressor effect with a myocardial-stimulating action in experimental studies."[1] "...Tens of thousands of intramuscular and subcutaneous injections. ... Not a single instance of tissue injury was observed."[2]

ARAMINE can be administered for pressor effect by any route—subcutaneous, direct intravenous, intramuscular, intravenous infusion. No slough reported **when injected into preferred vein of arm.** Minimal risk of causing arrhythmias.

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ARAMINE is a trademark of Merck & Co., INC.

Additional information is available to physicians on request.

1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762 (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

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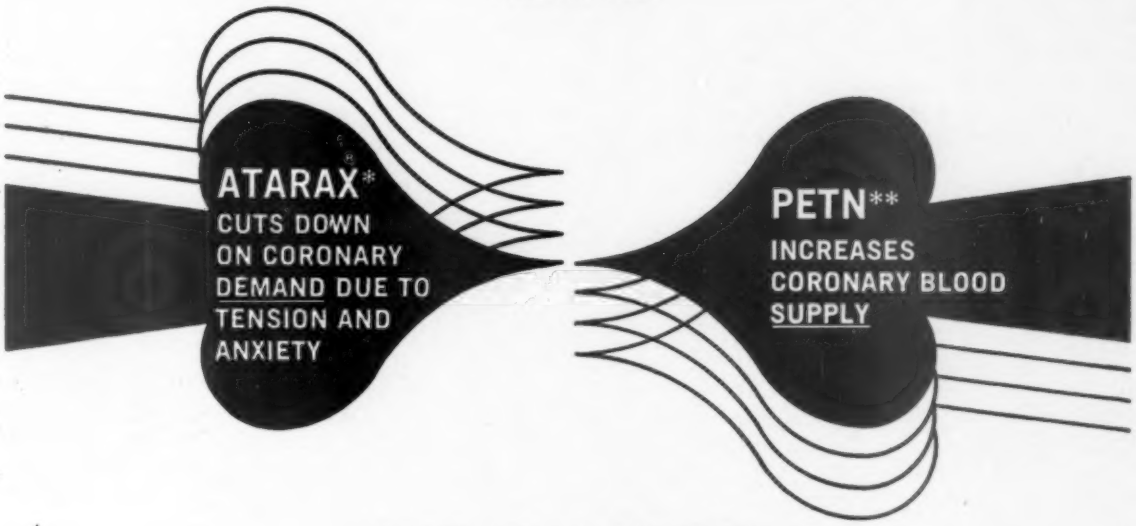

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they decrease "length, severity, and amount of angina pectoris" in anxious cardiacs.[1]

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dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. Atarax) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. Atarax). For convenience, write "CARTRAX 10" or "CARTRAX 20."
Supplied in bottles of 100. Prescription only.

1. Clark, T. E., and Jochem, G. G.: Angiology 11:361 (Aug.) 1960.

*brand of hydroxyzine **pentaerythritol tetranitrate

Roerig Rx

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Science for the World's Well-Being®

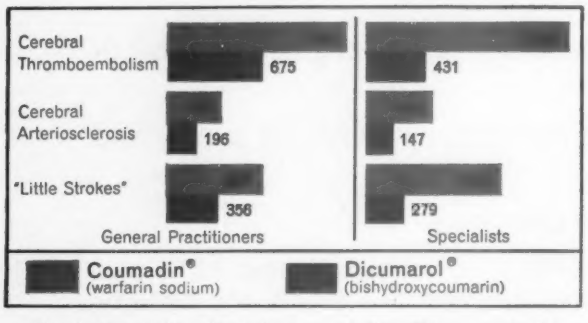
No. 3 of a series reporting on Endo Laboratories' Anticoagulant Survey

Nationwide Survey Explores Current Use of Anticoagulants in Cerebrovascular Disease

It has been estimated that there are 2,000,000 people suffering from vascular disease of the brain in the United States,[1] and that each year at least 500,000 persons are incapacitated by some kind of cerebral accident.[2] With the advancing age of our population, this problem is likely to increase.

As reported in previous numbers of this series, Endo Laboratories received replies to its comprehensive *Anticoagulant Survey* from a total of 10,016 physicians across the nation. Among the questions asked were—Are you now using oral anticoagulants for cerebral thromboembolism, cerebral arteriosclerosis, or "little strokes"—therapeutically, prophylactically? Without regard to the anticoagulant chosen, 14.4% of physicians reported use of oral anticoagulation in *therapy* of cerebral arteriosclerosis, 27.9% in little strokes, and 46.9% in cerebral thromboembolism. Anticoagulation was used *prophylactically* as follows: 10% in cerebral arteriosclerosis, 16.8% in little strokes, and 21.2% in cerebral thromboembolism.

Comparison of usage was also made among the 61.4% of reporting physicians prescribing Coumadin® most often and the 27.6% using Dicumarol®. (The remainder used indandiones [1.9%] and other anticoagulants.) The following graph shows the application of the leading anticoagulants *therapeutically* in cerebrovascular disease:

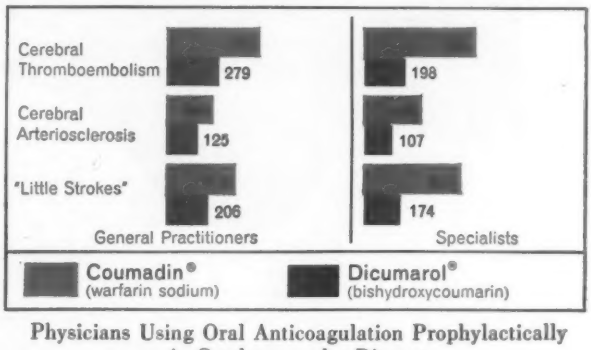


Physicians Using Oral Anticoagulation Therapeutically in Cerebrovascular Disease

Specialists Lead in Therapeutic Application of Anticoagulants

The analysis of the data presented in this survey indicates that 57% of the cardiologists and internists prescribing Coumadin—the most frequently prescribed oral anticoagulant—and 42% of the general practitioners used the drug therapeutically in cerebral thromboembolic disease. It is also noteworthy that 39% of the specialists used Coumadin in therapy of "little strokes" as compared with 22% of the general practitioners. Less frequent was its use as part of the therapy of cerebral arteriosclerosis—18% among the specialists and 12% among the general practitioners.

Anticoagulation was used less often for prophylaxis than for therapy of cerebral thromboembolism, little strokes, or cerebral arteriosclerosis, as shown in the following graph:



Physicians Using Oral Anticoagulation Prophylactically in Cerebrovascular Disease

Indications According to Recent Clinical Reports

Clinical experience emphasizes the need for careful diagnosis and patient selection before using anticoagulants in cerebral vascular disorders. Authorities are generally agreed that anticoagulants help to minimize the occurrence of attacks in patients with *transient ischemic episodes*,[3-6] which are "far more common than was previously suspected."[3] In addition, anticoagulation is advocated in the slowly evolving *stroke*,[5-7] i.e., "slow-onset" infarction. Evidence in cases of *cerebral embolism* indicates that anticoagulants may reduce the mortality rate. In patients with *completed cerebral infarction*, the findings of Thomes[8] indicate that long-term anticoagulant therapy may be valuable in minimizing recurrences and mortality rate. His results also suggest that "there is no time when it becomes safe to discontinue anticoagulant therapy."[8] Since the source of cerebral dysfunction may lie in occlusive disease of the carotid arteries in the neck, cerebral angiography is recommended as a valuable means of establishing the diagnosis.[1,2]

Physicians choosing Coumadin for anticoagulation have reportedly done so (see No. 1 of this series) because of its predictable effect, ease of maintenance, and single daily dose which permit a smoother, more convenient, and less hazardous anticoagulant regimen.

1. Meyer, J. S.: Am. J. Med. 30:577, 1961. 2. Kuhn, R. A.: Current M. Digest 28:51, 1961. 3. Groch, S. N., and Wright, I. S.: Circulation 23:458, 1961. 4. Siekert, R. G.; Millikan, C. H., and Whisnant, J. P.: J.A.M.A. 176:19, 1961. 5. Carter, A. B.: Neurology 11:601, 1961. 6. Marshall, J.: Ibid. 11:139, 1961. 7. Groch, S. N.: Ibid., p. 141. 8. Thomes, A. B.: Minnesota Med. 42:1587, 1959.

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Richmond Hill 18, New York

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"In a controlled clinical study of 260 postcoronary patients, one-half were given sublingual heparin and one-half received conventional treatment. During the period of observation, averaging more than 2 years per patient, there were 12 recurrent infarctions in the heparin-treated group and 38 in the control group. This difference is statistically significant."

Fuller, H. L.: Angiology *11*:200 (June) 1960.

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An informative booklet, "Hyperlipemia, Heparin and Management of the Postcoronary Patient," is available from Thos. Leeming & Co., Inc., 155 East 44th St., New York 17, N. Y.

*Registered trade mark. Patent applied for.

Clarin

(sublingual heparin potassium, Leeming)

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